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## DESCRIPTION

## CONTROLLED RELEASE PREPARATION

rechnical Field

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The present invention relates to a controlled release active which particular a capsule comprising a tablet, delays the migration speed in the gastrointestinal tract. polymer 성 the release gel-forming wherein ൻ and granule controlled fine 'n ļŝ preparation, ö ingredient granule

Background Art

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administration of οŧ designing have been developed from the viewpoint form which is used drug formulation. controlled release preparation, having a lot adrinistration 'n Lots the synthesize ď quite compound made with wherein agent's. g contriving efficacy with the such while sustained with the The ဌ pharmaceutical administration dosage are systems compound itself, is tried years. preparation by kinetics æ formulation is these release-controlled the dosage form of oral sustained drug day the oral among 딤 Ø ٦. ا day modify stage of release twice ğ for thereof frequently Ø twice improving cral ţ preparations 님 οŧ controlled synthetic attempts kinetics efficacy once Ŗ once or various most οŧ SS ξ

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gredient for an extended period of time by staying or slowly migrading in the gastraintestinal tract, is provided by means such as explaintly a tablet, granule or fine granule wherein the release of active ingredient is controlled and a gol-forming polymer. Said (57) Abstract: A controlled release preparation wherein the release of active ingredient is controlled, which releases an active intablet, granule or fine granule has a release-controlled coating-layer formed on a core particle containing an active ingredient. (57) Abstract: A controlled release preparation wherein the root greatent for an extended period of time by staying or slowly 10 greatent for an extended period of time by staying or slowly 10 greatent for an extended period of time by staying or slowly 10 greatent for the granule or fine granule or f

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preparation containing a medicament having an inhibitor action needs to be enteric-coated. That is, a composition containing a rapidly. In the case of a tablet, it is desirable to reduce a proton pump inhibitor to formulate into a granule or fine granule which has a broader surface area than a tablet and is easy to disintegrate or dissolve smal1 as acid-labile property as an active ingredient such the the size of tablet (for example, see JP-A 62-217322). dund to disintegrate rapidly in so the composition is preferred (hereinafter sometimes referred to as PPI) proton ď benzimidazole compound having compound having action is needed benzimidazole intestine, The

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After administered orally, the tablet, granule or fine tract with duodenum, jejunum, ileum and colon sequentially. And in the meantime, stomach, granule migrates through gastrointestinal to releasing an active ingredient

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extension of sustainability becomes possible by combining a the active ingredient is absorbed at the each absorption release of active is considered that a further release-controlled system with a function to control the is designed A controlled release preparation the gastrointestinal delaying It control the absorption by in some way. speed ingredient migration

disclosed in WO 01/89483, JP-R 2001-526213, USP 6,274,173, USP 6,093,734, USP 4,045,563, USP 4,686,230, USP 4,873,337, JSP 4,965,269, USP 5,021,433 and the like. 10

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such

Disclosure of Invention

Object of the Invention)

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An object of the present invention is to provide a οŧ active ingredient of drug is controlled, which releases an active ingredient for an extended period of time with staying or slowly migrating in the gastrointestinal tract. release preparation wherein the controlled release

Summary of the Invention)

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That is, the present invention provides:

(1). A capsule comprising a tablet, granule or fine ingredient active controlled and a gel-forming polymer; oť release granule wherein the

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(2) The capsule according to the above-mentioned (1), wherein the release of active ingredient is controlled by a release-controlled coating-layer formed on a core particle containing an active ingredient;

(3) The capsule according to the above-mentioned (2), wherein the release-controlled coating-layer contains a pH-dependently soluble polymer;

(4) The capsule according to the above-mentioned (2), wherein the release-controlled coating-layer is a diffusion-controlled layer;

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(5) The capsule according to the above-mentioned (1), wherein the release of active ingredient is controlled by dispersing an active ingredient into a release-controlled matrix composing tablet, granule or fine granule;

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or (4), wherein the tablet, granule or fine granule in which the release of active ingredient is controlled has a disintegrant layer containing disintegrant formed on the core particle containing an active ingredient and a release-controlled coating-layer formed on said disintegrant layer, and the release of active ingredient is initiated after a certain lag time;

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(7) The capsule according to any one of the above-mentioned (3) to (6), wherein the tablet, granule or fine granule in which the release of active ingredient is

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controlled is coated with a gel-forming polymer;

(8) The capsule according to the above-mentioned (7) which further contains a gel-forming polymer; (9) The capsule according to any one of the above-mentioned (1) to (7), which comprises two kinds of tablet, granule or fine granule having different release properties of active ingredient;

(10) The capsule according to the above-mentioned (9), which comprises a tablet, granule or fine granule having an enteric coat that releases an active ingredient at the pH of about 5.5 and a tablet, granule or fine granule having a release-controlled coating-layer that releases an active ingredient at the pH of about 6.0 or above:

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(11) The capsule according to the above-mentioned (1), (7) or (8), wherein the gel-forming polymer is a polymer whose viscosity of 5% aqueous solution is about 3,000 mPa·s or more at 25°C;

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(12) The capsule according to the above-mentioned (1), (7) or (8), wherein the gel-forming polymer is a polymer having molecular weight of 400,000 to 10,000,000;

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mentioned (2) to (4) or (6), wherein the release-controlled coating-layer is a layer containing one or more kinds of polymeric substances selected from the group consisting of hydroxypropylmethyl cellulose phthalate, cellulose acetate

copolymer, hydroxypropyl cellulose acetate succinate and acrylate-methyl methacrylate-trimethylammoniumethyl methacrylate chloride methacrylate copolymer, methyl methacrylate-ethyl acrylate copolymer, methacrylate-methacrylic acid copolymer, methacrylic acidmethyl cellulose, acrylate-methyl ethyl carboxymethylethyl copolymer, polyvinyl acetate phthalate; methacry\_ic acid-methyl acrylate phthalate,

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(14) The capsule according to the above-mentioned (13), wherein the release-controlled coating-layer is comprised 2 or more kinds of layers;

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has (15) The capsule according to the above-mentioned (1), wherein the release-controlled granule or fine granule a particle size of about 100-1,500 um; (16) The capsule according to the above-mentioned (1), wherein the active ingredient is a proton pump inhibitor (PPI);

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(17) The capsule according to (16), wherein the PPI is an imidazole compound represented by the formula  $(I^{\,\prime})$ :

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wherein ring C' is an optionally substituted benzene ring monocyclic aromatic substituted optionally an 占

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optionally substituted alkoxy group or an optionally substituted amino a salt heterocyclic ring,  $\mathbb{R}^0$  is a hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group,  $R^{1}$ ,  $R^2$  and  $R^3$  are the same or different and are a hydrogen atom, group, and Y represents a nitrogen atom or CH; or อท thereof or an optically active isomer thereof; group, an optionally substituted alkyl

(11), (18) The capsule according to the above-mentioned wherein the imidazole compound is lansoprazole; (19) The capsule according to the above-mentioned (17), of R-isomer active optically an 13 PPI lansoprazole; wherein 10

mentioned (1), (7) or (8), wherein the gel-forming polymer is one or more kinds of substances selected from the group carboxymethyl cellulose (CMC-Na), hydroxypropyl cellulose (20) The capsule according to any one of the abovemolecular weight: 100,000-10,000,000), hydroxypropylmethyl cellulose (HPMC), (HPC), hydroxyethyl cellulose and carboxyvinyl polymer; consisting of polyethylene oxide (PEO,

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polymer one of the above-400,000nentioned (1), (7) or (8), wherein the gel-forming weight: (21) The capsule according to any (molecular polyethylene oxide 10,000,000);

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(22) The capsule according to the above-mentioned (1) (8), wherein the gel-forming polymer or

powder, fine granule or granule;

(23) The capsule according to the above-mentioned (3), methy1 ïs polymer methacrylate-methacrylic acid copolymer; soluble wherein the pH-dependently

containing an imidazole compound represented by the formula (24) A tablet, granule or fine granule wherein the core particle release of active ingredient is controlled, said tablet, comprising a granule fine ٥ĸ

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thereof or an optically active isomer thereof as an active optionally substituted alkoxy group or an optionally substituted amino wherein ring C' is an optionally substituted benzene ring monocyclic optionally or a salt 'n, R<sup>2</sup> and R<sup>3</sup> are the same or different and are a hydrogen atom, substituted aralkyl group, acyl group or acyloxy group, or CH; пe an aromatic a hydrogen atom, an optionally substituted alkyl group, group, and Y represents a nitrogen atom substituted 13 optionally heterocyclic ring,  $R^0$ an. or

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pH-dependently soluble release-controlled coating-layer substance polymeric οĘ comprises one kind which

ingredient, and

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dnoxb hydroxypropyl sellulose acetate succinate, polyvinyl acetate phthalate and shellac, and said polymeric substance is soluble in the mixture of two or more kinds of polymeric substances having methyl methacrylate-methacrylic acid copolymer, methacrylic methacrylic acid-methyl cellulose acetate phthalate, carboxymethylethyl cellulose, phthalate, the cellulose from copolymer, selected of hydroxypropylmethyl acid-ethyl acrylate copolymer, properties methacrylate release acrylate-methyl consisting different

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(25) The tablet, granule or fine granule according to the pH-dependently intermediate layer which is formed on a core particle; soluble release-controlled coating-layer is formed wherein (24), the above-mentioned

pH range of 6.0 to 7.5;

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g (26) The capsule comprising the tablet, granule (24); fine granule according to the above-mentioned

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granule or fine granule containing a fine granule according to the above-mentioned (24) and an H (27) The capsule comprising the tablet, granule compound represented by the formula (I'); enteric-coated tablet,

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ဌ the above-mentioned (24), wherein the active ingredient is (28) The tablet, granule or fine granule according lansoprazole;

above-mentioned (24), wherein the active ingredient is (29) The tablet, granule or fine granule according to the

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optically active R-isomer of lansoprazole;

- (30) The tablet, granule or fine granule according to the above-mentioned (24), wherein the active ingredient is an optically active S-isomer of lansoprazole;
- (31) The tablet, granule or fine granule according to the above-mentioned (24), wherein the active ingredient is a derivative of lansoprazole;

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(32) The tablet, granule or fine granule according to the above-mentioned (24), wherein the active ingredient is a derivative of optically active R-isomer of lansoprazole;

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any one of the above-mentioned (24), (25) or (28) to (32), comprising having an enteric coat on the core particle containing an active ingredient, a disintegrant layer containing disintegrant on said enteric coat and a release-controlled coating-layer on said disintegrant layer;

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- (34) The tablet, granule or fine granule according to any one of the above-mentioned (28) to (33), which is coated with a gel-forming polymer;
- (35) An extended release capsule comprising the tablet, granule or fine granule according to any one of the abovementioned (28) to (32) and a gel-forming polymer;

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(36) A tablet, granule or fine granule according to the above-mentioned (24) wherein the release of active ingredient is controlled by two or more kinds of release-

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controlled coating-layers, and the outermost release-controlled coating-layer is soluble at higher pH than the inner release-controlled coating-layer;

the above-mentioned (36), wherein the inner release-controlled coating-layer is soluble in the pH range of 6.0-7.0 and the outermost release-controlled coating-layer is soluble at the pH of 7.0 or above;

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the above-mentioned (36), wherein the inner release-controlled coating-layer is soluble in the pH range of 6.5-7.0 and the outermost release-controlled coating-layer is soluble at the pH of 7.0 or above;

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(39) The tablet, granule or fine granule according to the above-mentioned (36), wherein the thickness of the outermost release-controlled coating-layer is 100 µm or less;

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(40) The granule or fine granule according to the above-mentioned (36), wherein the release-controlled granule or fine granule has a particle size of about 100-1,500 µm;

- (41) A capsule comprising
- (i) a tablet, granule or fine granule in which the release of active ingredient is controlled; said tablet, granule or
- 25 fine granule comprises

a core particle containing an imidazole compound represented by the formula (I'):

wherein ring C' is an optionally substituted benzene ring optionally substituted alkoxy group or an optionally substituted amino salt thereof or an optically active isomer thereof as an active optionally monocyclic substituted aralkyl group, acyl group or acyloxy group,  $\mathbb{R}^1,$ and R³ are the same or different and are a hydrogen atom, or a group, and Y represents a nitrogen atom or CH; an is a hydrogen atom, an aromatic ar optionally substituted alkyl group, substituted heterócyclic ring, R<sup>o</sup> optionally ingredient, and an ö

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the group methyl methacrylate-methacrylic acid copolymer, methacrylic a pH-dependently soluble release-controlled coating-layer mixture of two or more kinds of polymeric substances having cellulose acetate phthalate, carboxymethylethyl cellulose, acid-ethyl acrylate copolymer, methacrylic acid-methyl hydroxypropyl phthalate, or polymeric substance different release properties selected from hydroxypropylmethyl cellulose copolymer, methacrylate οĘ which comprises one kind acrylate-methyl of consisting

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cellulose acetate succinate, polyvinyl acetate phthalate and shellac; said polymeric substance is soluble in the pH range of 6.0 to 7.5, and

(ii) a tablet, granule or fine granule comprising a core particle containing an active ingredient and enteric coatwhich is dissolved, thereby an active ingredient being released in the pH range of no less than 5.0, nor more than

6.0 ;

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- wherein the pH-dependently soluble release-controlled coating-layer is formed on an intermediate layer which is formed on the core particle containing an active ingredient;
- (43) The capsule according to the above-mentioned (41), wherein the active ingredient is lansoprazole;

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- (44) The capsule according to the above-mentioned (41), wherein the active ingredient is an optically active R-isomer of lansoprazole;
- (45) The capsule according to the above-mentioned (41), wherein the active ingredient is an optically active Sisomer of lansoprazole;

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- (46) The capsule according to the above-mentioned (41), wherein the core particle containing an active ingredient contains a stabilizer of basic inorganic salt;
- (47) The capsule according to the above-mentioned (41),

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wherein the pH-dcpendently soluble release-controlled coating-layer of the tablet, granule or fine granule in which the release of an active ingredient is controlled is a layer soluble in the pH range of no less than 6.5, nor more than 7.0;

wherein the pH-dependently soluble release-controlled coating-layer contains a mixture of two or more kinds of methyl methacrylate-methacrylic acid copolymers having different release properties; and

(49) The capsule according to the above-mentioned (41), which further contains a gel-forming polymer.

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(Detailed Description of the Invention)

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granules.

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composition containing a tablet, granule or fine granule wherein the release of active ingredients is controlled, or granule or fine granule and a gel-forming polymer which in particular. It has been cleared that the persistence of present invention relates to a pharmaceutical delays digestive tract migration speed. The pharmaceutical or a capsule filled in capsule, but a capsule is preferred tablet, composition of the present invention may be these tablet, tablet, granule or fine granule and a gel-forming polymer, or a form of a mixture of these containing composition granule itself, pharmaceutical granule or fine The

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blood levels after oral administration is remarkably prolonged by these combinations.

"tablet, granule or fine granule wherein the release of coated with a usual enteric coat which is dissolved at a pH granule with a layer controlling the release of active ingredient, or by dispersing the active of the present invention of about 5.5, and tablets containing these granules or fine active performed by coating the active ingredient in a tablet, release control of active ingredient in "a tablet, present invention which Further, ٥Ę granule relcase ingredient in release-controlled matrices. granule or fine granule wherein the of the active ingredient is controlled" ingredient is controlled" a tablet, fine granule or fine include also or granule

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dissolved at a pH of about 5.5, and a diffusion-controlled dissolved and which active ingredient through pores which are It does not include a usual enteric such as a pH-dependently soluble layer which is dissolved at a higher pH region than a usual enteric coating which is the "release-controlled it indicates a coating-layer having a function of further specification, delaying or extending the release of active ingredient, present layer whose layer itself is not in the wher is mentioned hand, formed in the layer. other coating-layer" the releases an

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means 5.5, Clark-Lubs solution. Further, the pH mentioned here means rapidly dissolved in the intestinal juice and release of about Hereinafter, the pH of a pH-dependently soluble layer at a pH or coat and layer which is dissolved solution the pH of these solutions. Mcilvaine active ingredient. the oĘ Нď

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core the or layer but also the coating layers in which a part is coated (coating-layer which covers inlcudes coating layers in a film form and those the coating-layer includes inner the coating-layer of the "release-controlled coatingthe inner core or layer is not covered but most of at least about 80% or more of the surface of the inner or layer, and preferably covers the surface entirely). not only a coating-layer which entirely coats the Also, having larger thickness. inner core or layer layer"

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absorption from the digestive tract of the active the of the present invention, the composition containing a gel-forming polymer forms adhesive gels by rapidly absorbing water by systems or their retentive prolongation in the digestive tract of a tablet, controlled release tablet, granule or fine granule and (2) utilizing (1) a release control of active ingredlent by oţ combinations. Among the pharmaceutical composition οŧ composition polymer, present invention is controlled by two kind granule or fine granule by a gel-forming pharmaceutical the from ingredient The

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a controlled system, and as a result, the incidences of þe gradually migrated through the digestive tract. The release pulsatile manner from the tablet, granule or fire granule the gel-forming polymer in the digestive tract when orally granule ij t t of active ingredient is controlled in the meanwhile, the gels released continuously or fine Ę administrated, and the tablet, granule or gels or surface of active ingredient is theö retained ģ

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therapeutic ð controlling the release of side effects as well The above-mentioned system enabling the persistence caused by initial rise of blood level and the like, οĘ effectiveness at a low dose and recuction advantages as the reduction of administration times. cherapeutic effective levels by has time long Ø

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attained

prolonged absorption and drug efficacy are

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Such 1.5 οĘ polymer is gel-forming contacting with water and agueous gel-forming The gel-forming polymer may be a polymer which rapidly polymer is preferably a polymer having polymer preferably a polymer usually having a molecular weight prolongs the retention time in the digestive tract. 5° gel-forming As the granular for The of about 3000 mPa·s or more formulations. about 400000 to 10000000 in general. polymer, powder, granular or fine the forms highly viscous gels by Further, producing 25°C. preferable for solution at gel-forming viscosity

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15 Ŋ 10 carboxyvinyl polymer and the like are preferably used as a (HIVISWAKO (R) 103, 104 and 105 manufactured by Wako Pure Goodrich Co., Ltd.), chitosan, sodium alginate, pectin and as a mixture of at an appropriate Na, Sanlose F-1000MC), hydroxypropyl cellulose (HPC, for polymer Chemical Industries Ltd.; CARBOPOL 943 manufactured by CMC-Na, Metlose 90SH50000, and Metlose 90SH30000; manufactured by manufactured by Nippon Soda Co., Ltd.), (molecular weight: 7000000), Polyox WSR 301 Polyox WSR N-60K (molecular weight: Chemical Co., Ltd.), nydroxypropyl methylcellulose (HPMC, Metlose 90SH10000, Shin-Etsu Chemical Co., Ltd.), carboxymethylcellulose (CMCfor example, (molecular weight: 5000000), Polyox WSR (molecular HPC, carboxyvinyl polymer includes a polyethylene oxide (PEO, proportion. In particular, PEO, HPMC, by mixing at weight: 2000000), and Polyox WSR 205 be used alone or Dow (HEC) least 2 or more of powders (molecular weight: 4000000), 500000); manufactured by cellulose the like. These may gel-forming polymer. example, HPC-H, 303 hydroxyethyl Polyox WSR Coagulant

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core particle containing at least one active fine or fine granule ingredient is coated with a release-controlled coatingactive ingredient or granule controlled includes a tablet, granule a tablet, oŧ granule wherein the release of One preferable form wherein

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an core can be produced centrifugal γď freund Industrial Co., Ltd.) or a centrifugal fluidized coating may be carried out by dusting an active ingredient For example, they can be For (particle 500-355), NONPAREIL-105 300-180); manufactured by Freund Industrial Co., Ltd.) and Celphere (CP-507 (particle diameter: 500-710), and CP-305 (particle Kasei these granules or fine granules; or the particle obtained by an exciptent Further, ingredient is coated on a core which is an inactive carrier granule or fine granule, as a core particle can be used the active such as NONPAREIL (NONPAREIL-101 (particle diameter: 850granules. In order to prepare such core-possessing tablet, particle is prepared by coating manufactured active ingredient on a core of an inactive carrier, produced by the method disclosed in JP-A 63-301816. ٥Ľ using Asahi ä granules 500-355), NONPAREIL-103 granulator (POWREX MP-10), or the like. and wherein granulation using an active ingredient and prepared by for example, particles containing an active ingredient ģ CF-360, 500-355 a tablet containing these granule manufactured and flùid-bed granulator (CF-mini, diameter: 710-500, Corporation); or the tablet formulation. using, 710-500, fine example, when a core granulation, 300-500); 710-500, and ٥Ľ diameter: 850-710, for granule usually used (particle layer and diameter: vet tablet, coating ρλ 20

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granulator, a wet extruding granulator, a alcohol, Macrogol, Pullronic F68, gum arabic, gelatin and if necessary, adding disintegrants such as sodium FMC International Co., Ltd.), polyvinyl particle can be produced by granulating excipient as lactose, white sugar, mannitol, corn starch and active ingredient, using a polyvinyl to produce them active ingredient may be coated at two steps by carrying out the coating using the above-mentioned two apparatuses calcium carboxymethyl cellulose, while adding a solution containing a binder and the like on methylcellulose, (Ac-Di-Sol, pyrrolidone and low substituted hydroxypropyl cellulose, not limited and for example, in combination. When an inactive carrier core is not used, an inactive carrier with spray and the like. using a centrifugal fluid-bed granulator and the like. hydroxypropyl cellulose, methyl cellulose, cellulose is preferable in the latter coating hydroxypropyl fluidized bed granulator and the like. an carboxymethyl The production apparatuses are and carboxymethy] cellulose, crystalline cellulose g 8 manufactured by a stirring such cross core of starch, sodium a core such with ij

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Particles having desired sizes can be obtained by sieving the granules or fine granules obtained. The core particle may be prepared by dry granulation with a roller compactor and the like. Particles having a particle size

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21 to 5 mm, preferably 100 µm to 3 mm and more

are used

to 2 mm

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preferably 100

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controlled coating-layer when the active ingredient is an of drugs that the intermediate coating layer particle. It is preferable from the viewpoint of improving core particle thus to provide an intermediate active such as PPI and the like, releaseformed by Ø direct contact of as the pe nsed þe with may active ingredient-containing coating layer, and the particle may The intermediate coating layer ingredient-containing core particle unstable drug against an acid, the obtained may be further coated is provided to intercept plural number of layers. the stability Ŋ 50

starch, lactose, sugar alcohol (D-mannitol, erythritol and and hydroxyethyl methylcellulose with saccharides such as sucrose [purified sucrose (pulverized (powdered sugar), not masking agents alcohol, methylcellulose The coating materials for the intermediate coating layer include those obtained by appropriately compounding polymeric materials such as low substituted hydroxypropyl hydroxypropyl like), pulverized) and the like], starch saccharide such antistatic  $\mathsf{the}$ and example, cellulose, the like) and TC-5 polyvinyl Excipients (for methylcellulose (for example, hydroxypropyl and polyvinylpyrrolidone, (titanium oxide sellulose, the like).

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titanium oxide, talc and the like) may be suitably added

mentioned below, if necessary.

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components of the intermediate coating layer are diluted The coating can be carried outthe to carry out the coating while The coating amount of the intermediate coating layer is usually about 0.02 part by weight to about 1.5 parts by weight based on 1 part by weight of granules containing an active ingredient, and preferably about 0.05 part by weight purified water and sprayed to coat in liquid form. For example, preferably, cellulose. spraying a binder such as hydroxypropyl to about 1 part by weight. by conventional methods. preferable 13 ij with

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fine pH-dependently dissolved/eluted to control the release, and release-controlled coating-layer, or the tablet containing these controlled release granules or fine granules. Herein, the coating material is certain pH value to release an active ingredient. A usual enteric coat is eluted at a pH of about 5.5 to initiate the granule contained in the pharmaceutical composition of the mentioned core particle with a coating material which is is preferable to coat the aboveto prepare the tablet, granule or fine granule having dissolved/eluted under the circumstances of more than or granule the controlled release tablet, the "pH-dependently" means that present invention, it As

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release of drug, while the coating material of the present invention is preferably a substance which is dissolved at a higher pH (preferably a pH of 6.0 or above and 7.5 or below, and more preferably a pH of 6.5 or above and below 7.2) and controls more favorably the release of drug in the stomach.

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1100 the release of medical active ingredient, polymers such as (CMEC **S100** have As a coating material for controlling pH-dependently manufactured by Shin-Etsu Chemical Co., Ltd.), cellulose methyl methacrylic acid-ethyl acrylate copolymer (Eudragit 1100-55 or Eudragit 130D-55 (methacrylic acid copolymer LD); manufactured by Rohm Co.), Rohm Co.), (HPMCAS Co., Ltd.), polyvinyl ranule or fine granule may be those having two or more methacrylic acid copolymer S); manufactured by Rohm Co.), methacrylate The tablet, active ingredient. release-controlled coating-layers which ethylcellulose (Eudragit Eudragit (HP-55, Freund Industrial Co., Ltd.), succinate γq acrylate-methyl scetate phthalate and shellac are used. copolymer (Eudragit FS30D manufactured phthalate copolymer or. dried methacrylic acid copolymer LD) acetate î acetate phthalate, carboxymethyl Chemical οŧ acid copolymer methylcellulose properties Shin-Etsu acid-methyl cellulose methacrylate-methacrylic acid release γď manufactured by hydroxypropyl hydroxypropyl nethacrylic nanufactured (methacrylic οŧ different kinds

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of pH 6.8.

polymer as the above-mentioned coating material may be used

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the polymers may be

alone or at least 2 or more kinds of

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methylcellulose (HPMC, Metlose 9CSH1000C, Metlose 90SH50000, Co., Ltd.), hydroxypropyl HPC-H hydroxyethyl 104, 105: manufactured by Wako Pure Chemical Industries manufactured by Goodrich Co., Ltd.), on the ö 2000000), and Polyox WSR 205 (molecular weight: 600000); fine granule wherein a material which becomes viscous by contact with water, such as polyethylene oxide (PEO, for example, Polyox (molecular weight: 7030000), Polyox WSR Coagulant (molecular weight: 4000000), Polyox WSR N-60K (molecular weight: cellulose (HEC), carboxyvinyl polymer (HIVISWAKC (R) 103, The controlled release tablet, granule or fine granule a controlled Ltd.), carboxymethyl cellulose (CMC-Na, Sanlose F-1000MC), detlose 90SH30000; manufactured by Shin-Etsu Chemical Co., granule coated example, 301 active ingredient release-controlled tablet, simply as release granule) may be a tablet, granule or Ltd.), 15 5000000), Polyox WSR for pectin, . ც ţ (HPC, sometimes referred chitosan, sodium alginate and Nippon Soda Chemical fine granule thus obtained. celulcse Dow Ltd.; CARBOPOL 943 (molecular weight: ρλ ρλ hydroxypropyl manufactured (hereinafter, manufactured WSR 303 20 15 S 10

The controlled release granule may be a form in which the core particle containing an active ingredient is coated with a diffusion-controlled layer having an action of

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layers. It is desirable that the coating material is used more desirably, a polymer soluble at a pH of 6.0 or above and a 7.0 or above are used in combination at a ratio of 1 : 0.5 nsed in at a pH of 6.0 or above and a polymor soluble at a pH of more Further, more soluble or at least 2 or more kinds of the polymers may be coated secuentially to prepare multialone or, if necessary, in combination so that the polymer 6.0 or above, and further combination, and furthermore desirably, a polymer above are above. above, of or 7.0 or Hd or ø 6.75 οĘ 6.5 at used to coat in combination, 펎 preferably ij of 떮 ЬH at æ ๗ polymer soluble preferably at preferably at dissolved to 1:5.E.

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Further, plasticizers such as a polyethylene glycol, dibutyl sebacate, diethyl phthalate, triacetin and triethyl citrate, stabilizers and the like may be used for coating, if necessary. The amount of coating material is 5% to 200% based on the core particle, preferably 20% to 100% and more preferably 30% to 60%. The rate of elution of active ingredient from the active ingredient release-controlled tablet, granule or fine granule thus obtained is desirably 10% or less for 5 hours in a solution of pH 6.0, and 5% or less for one hour and 60% or more for 8 hours in a solution

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Rohm Co.), ethyl cellulose and the The materials for these diffusion-controlled Layer include methacrylate-trimethylammoniumethyl like. Further, these materials for layer may be mixed at an mixing with (aminoalkyl methacrylate copolymer RL); manufactured by Rohm Co.), acrylate copolymer (Eudragit HPC, controlling the release of active ingredient by diffusion. (aminoalkyl 6300, lactose, as HPMC, Æ RS ργ copolymer (Eudragit carboxyvinyl polymer, polyethylene glycol methacrylate copolymer RS) or Eudragit pore forming substances such mannitol and organic acid at a fixed ratio. appropriate ratio, and can be used methyl methacrylate-ethyl ethyl acrylate-methyl methacrylate chloride NE30D manufactured by hydrophilic

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Further, in order to prepare the tablet, granule or fine granule wherein the release of active ingredient is disintegrant layer is provided between the core particle containing an active ingredient and the release-controlled coating-layer by coating a swelling substance such as a disintegrant previously before coating the above-mentioned preferably, a swelling substance such as cross carmelose sodium (Ac-Dicarmelose CROSSPOVIDON (ISP Inc.) and low substituted hydroxypropyl calcium (ECG 505, manufactured by Gotoku Chemicals Co.), time, lag International Co.), example, fixed æ For initiate after diffusion-controlled layer. E G manufactured by ţ controlled Sol,

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methacrylate

acrylate-methyl

acid-methyl

methacrylic

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Ltd.), diffusion-controlled layer which is prepared by mixing at a S100 fixed ratio one or more kinds of polymers selected from nethacrylate chloride copolymer (Eudragit RS or Eudragit dried methacrylic acid copolymer LD) or Eudragit L30D-55 cellulose (L-HPC manufactured by Shin-Etsu Chemical Co., Ltd.) is primarily coated on a core particle, and then the thyl acrylate-methyl methacrylate-trimethylammoriumethyl manufactured by Rohm Co.), methyl methacrylate-ethyl manufactured by Rohm Co.), ethyl cellulose and the like; with hydrophilic pore polyethylene glycol 6000, lactose, mannitol and an organic enteric cellulose acetate phthalate, carboxymethyl ethylcellulose (CMEC; manufactured by Freund Industrial Co., Ltd.), methyl (Eudragit L100 methacrylic acid copolymer S); manufactured by Rohm Co.), methacrylic acid-ethyl acrylate copolymer (Eudragit L100-55 methacrylic acid copolymer LD); manufactured by Rohm Co.), orming substances such as HPMC, HPC, carboxyvinyl polymer, polymers which release pH-dependently an active ingredient, as hydroxypropyl methylcellulose phthalate (HP-55, HPcoated with Eudragit pe . ვ may Chemical secondarily copolymer material or acrylate copolymer (Eudragit NE30D ਜ Shin-Etsu nethacrylate-methacrylic acid (methacrylic acid copolymer coating particle is ρλ The secondary manufactured coated resulting acid. ιU 10 15 20

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coating material is 1% to 100% . 0 Co., Ltd.), polyvinyl (HPMCAS; Rohm to 200% based on the core particle, preferably 20% succinate manufactured by acetate Chemical acetate and shellac. The amount of and more preferably 30% to 60%. copolymer (Eudragit FS30D; Shin-Etsu cellulose ρλ hydroxypropyl manufactured

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HPC-H 303 manufactured by Dow Chemical Co., Ltd.), hydroxypropyl methylcellulose (H?MC, Metlose 90SH10000, Metlose 90SH50000, Co., Ltd.), hydroxyethyl Chemical Industries (molecular weight: 2000000), and Polyox WSR 205 (molecular weight: 600000); sepacate, diethyl phthalate, triacetin and triethyl citrate, necessary. The controlled release tablet, granule or fine be a tablet, granule or fine granule wherein a (molecular manufactured by Shin-Etsu Chemical Co., cellulose (HEC), carboxyvinyl polymer (HIVISWAKO (R) 103, contact with water, such polyethylene glycol, dibutyl Coagulant Ltd.), carboxymethyl cellulose (CMC-Na, Sanlose F-1000MC), coating, polyethylene oxide (PEO, for example, Polyox WSR examble, 301 Polyox WSR for weight: 5000000), Polyox WSR pe nseq for 104, 105: manufactured by Wako Pure N-60K material which becomes viscous by (molecular weight: 7000000), cellulose (HPC, by Nippon Soda WSR stabilizers and the like may ช Polyox such Metlose 90SH30000; 4000000), Plasticizers hydroxypropyl manufactured granule may (molecular weight:

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the or Ltd.; CARBOPOL 943 manufactured by Goodrich Co., Ltd.), granule 6 is coated tablet, pectin, active ingredient release-controlled chitosan, sodium alginate and fine granule thus obtained.

up between said granule having 2 or coating-layers having different release properties of active ingredient, a layer structure containing an active ingredient between coating an active ingredient on the tablet, granule or fine granule wherein the relcase of active ingredient is controlled by release-controlled coating-layers. A form of these multipresent tablet, release-Ø the with the controlled coating-layer of the present invention. is prepared by includes ŏĘ containing an active ingredient may be set invention, followed by further coating coating-layer In the tablet, granule or fine more kinds of release-controlled ccating-layers granule or fine granule which release-controlled release-controlled layer the 15 ιΩ 12

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dispersing the active ingredients into hydrophobic carriers such as waxes such as hardened castor oil, hardened rape granule or fine be produced by homogeneously active grantle release-controlled matrix. These controlled release tablet, granule in which the active ingredients are dispersed in Another form of the tablet, granule or fine the οĘ one ingredients is controlled may be a tablet, east at granule or fine granule can οŧ release  $\mathsf{the}$ wherein

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and usually used for preparation of a drug may be dispersed powders of with water may be dispersed into the matrix together with which the active ingredients are homogeneously dispersed mannitol, .corn starch and crystalline cellulose which are acid polymer chitosan and the like which form viscous gels by contact polyglycerin fatty acid ester. The matrix is a composition lactose, CARBOPOL), HPMC, HPC, alcohol, 88 If necessary, excipients such cross-linked acrylic Further, stearyl the active ingredients and excipients. and 105, and active ingredients. acid (HIVISWAKO (R) 103, 104 polyoxyethylene oxide, stearic in a carrier. oil, the seed 넊

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melt As the preparation method, they can be prepared by spray chilling and spray dry, a s methods such granulation.

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The controlled release tablet, granule or fine granule 303 Coagulant methylcellulose (HPMC, Metlose 90SH10000, Metlose 90SH50000) may be a tablet, granule or fine granule wherein a material such as weight: 4000000), Polyox WSR N-60K (molecular weight: 2000000), and Polyox WSR 205 (molecular weight: 600000); Co., Ltd.), hydroxypropyl (molecular WSR which becomes viscous by contact with water, Polyox 301 WSR 5000000), Polyox WSR examble, Polyox for ,(0000001 manufactured by Dow Chemical polyethylene oxide (PEO, weight: (molecular weight: (molecular

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Metlose 90SH30000; manufactured by Shin-Etsu Chemical Co.,

Ltd.), hydroxyethyl 104, 105: manufactured by Wako Pure Chemical Industries on the fine granule thus obtained. These materials which become viscous by contact with water may be coexisted in one well as using Ltd.; CARBOPOL 943 manufactured by Goodrich Co., Ltd.), Ltd.), carboxymethyl cellulose (CMC-Na, Sanlose F-1000MC), cellulose (HEC), carboxyvinyl polymer (HIVISWAKO (R) 103, granule is coated example, active ingredient release-controlled tablet, preparation such as a capsule and the like as for pectin, . 8 (HPC, and Soda algirate cellulcse Nippon φ socium hydroxypropyl manufactured chitosan, for coat.

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The tablet, granule or fine granule of the present invention wherein the release of active ingredient is controlled may be a form having the above-mentioned various coating-layers, controlled matrixes and the like in combination. release-controlled οĘ kinds

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As the size of tablet, granule or fine granule wherein release of active ingredient is controlled, particles 5 mm, preferably 100 µm mm are used. ξ Granules or fine granules having a particle size to 3 mm and more preferably 100 µm to 2 um to 1500 µm are most preferred. having a particle size of 50 µm to

Further, additives such as excipients for providing

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wheat starch, rice sodium alginate, pullular, gum arabic powder, gelatin and the like), disintegrants (for example, low substituted acid, malic acid, aspartame, acesulfam potassium, thaumatin, glutamate, sodium 5'-inosinate, sodium 5'-guanylate and the like), surfactants (for example, polysolvate (polysolvate the like), lubricants (for example, magnesium crosspovidon, hydroxypropylstarch and the like), flavoring agents (for example, citric acid, ascorbic acid, tartaric sodium polyoxyethylene-polyoxypropylene perfumes menthol, peppermint carboxymethyl cellulose sodium, partial  $\alpha$  starch,  $\alpha$  starch, anhydride, carbonate, calcium silicate, and the like), binders (for example, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, methyl cellulose, polyvinyl alcohcl, like), lactose, trehalose, calcium, sodium, stearate, sucrose fatty acid eater, sodium stearylfumarate, sodium laurylsulfate and the like), fructose, 'dipotassium, carmelose carmelose calcium silicic acid glycol and multitol, corn starch, potato starch, glucose, sedimented (for example, lemon oil, orange oil, carmelose, cross erythritol, glycylrrhizin polyethylene cellulose, (for example, sodium, metaphosphorate, cellulose, like), D-mannitol, talc, crystalline carboxymethylstarch sodium, the hydroxypropyl stearic acid, preparations copolymer, saccharin sorbitol, and and sucrose, calcium starch, oi1 80

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colorants (for example, titanium oxide, edible Yellow No.5, edible Blue No.2, iron (III) oxide, yellow iron (III) oxide, and the like), antioxidants (for example, sodium ascorbate, L-cysteine, sodium bisulfate, and the like), masking agents (for example, titanium oxide and the like), and antistatic agents (for example, talc, titanium oxide and the like) can be used.

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The particle diameter of raw materials used here are not particularly limited, and particles having a diameter of about 500 µm or less are preferred from the viewpoint of productivity and dosing.

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forming polymer being retentive in the digestive tract is tablet, granule or fine granule thus obtained may be administrated as it is by mixing with a digestive tract gelto 50%, more release tablet, formulated as preferably 10% to 40%, and further more preferably 10% the capsule by filling in capsules. The amount of 28 retentive gel-forming polymer, or can be the controlled or fine granule, preferably 0.1% to 100% relative to granule 35%

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present invention thus obtained is a composition having a extended activity of drug by a release-controlled system wherein further hours, and the least more preferably 12 hours οŧ at composition revealed for pharmaceutical ر ا 8 hours, therapeutic effect preferably

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preferably 16 hours.

efficacy. Exemplified are anti-inflammatory drugs such as indomethacin and acetaminophen, analgesics such as morphine, antitumors such as fluorouracil and aclarubicin, narcotics such as midazolam, anti-hemostasis agents such as ephedrine, codeine, antiarrythmic agents such as quinicine and dizoxin, of drug active ingredients are not particularly limited, bronchodilators such as theophyline, antitussives such as tolbutamide, pioglitazone and acid, anticonvulsants such as phenitoin, local anesthetics such hydrocortisone, drugs effective for central nerve such as eisai, hypolipidemic drugs such as pravastatin, antibiotics such as amoxicillin and cephalexin, digestive tract blockers such as famotidine, ranitidine and cimetidine gastritis, symptomatic cardiovascular agonists such as diazepam and diltiazepam, maleate, diuretics such as hydrochlorothiazide and furosemide, gastroesophageal reflux disease, and gastric and duodenal represented by lansoprazole and optically active isomers ulcers, and benzimidazole proton pump inhibitors (PPI) exitomotory agents such as mosapride and cisapride, such ascorbic region chlorophenylamine hormones the a S oţ can be applied irrespective adrenocortical vitamins such remedies of ผ as such such are the lidocaine, antihistamines troglitazone, antidiabetics which 93

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thereof (R-isomer and S-isomer, preferably R-isomer (hereinafter, occasionally referred to as Compound A)), omeprazole and optically active isomers:

S omeprazole), rabeprazole and optically active isomers thereof, pantoprazole and optically active isomers thereof and the like, and imidazopyricine PPI represented by tenatoprazole and the like.

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According to the present invention, the preparations the following acid-labile which contain, as an active ingredient, a PPI such as acideneral formula (I') such as lansoprazole and optically following Cormula (I), and relatively acid-stable imidazole compound derivatives (prodrug type PPI) represented by the following active isomers thereof have an excellent sustainability of or salts thereof or optically drug efficacy. As a result, dosing compliance is also the partícular, labile imidazole compounds represented by improved and therapeutic effect is increased. benzimidazole compounds represented by 'n general formula (II) or (III) thereof, isomers active

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Wherein ring C' indicates a benzene ring optionally having a substituent group or an aromatic monocyclic heterocyclic

and R are the same or different and indicate a hydrogen an alkoxy group optionally having a substituent group or an substituent group, an acyl group or an acyloxy group;  $\mathrm{R}^1,$ atom, an alkyl group optionally having a substituent group, group, ring optionally having a substituent group;  $\mathbb{R}^0$  indicates optionally having substituent respectively; and Y indicates a nitrogen atom or CH. Ø aralkyl group group optionally having hydrogen atom, an

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Among the compounds represented by the above-mentioned 18 penzene ring optionally having a substituent group formula (I'), the compound in which the ring C' particularly represented by the following formula (I)

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Namely, in the formula (I), ring A indicates a benzene and Y have the same meaning as in the above-mentioned ring optionally having a substituent group, and  $R^0$ ,  $R^1$ , formula (I').

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In the above-mentioned formula (I), the preferable compound is a compound wherein ring A is a benzene ring which may have a substituent group selected from a halogen group, an optionally halogenated  $C_{1-\varepsilon}$  alkyl atom,

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9 an acyl group or an is a hydrogen atom, a  $C_{1-\epsilon}$  alkoxy- $C_{1-\epsilon}$  alkoxy group, or an acyloxy group; R¹ is a C₁-¢ alkyl group, a C₁-6 alkoxy group, a C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> alkoxy group or a di-C<sub>1-6</sub> alkylamino group; nembered heterocyclic group; R° is a hydrogen atom, optionally halogenated  $C_{1-4}$  alkoxy group and a 5- or atom or a C1-6 alkyl group, and Y is a nitrogen atom <u>س</u> optionally halogenated  $C_{1-6}$  alkoxy group; optionally substituted aralkyl group,

In particular, the preferable compound is a compound represented by the formula (Ia);

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wherein  $\mathbb{R}^1$  indicates a  $C_{1-3}$  alkyl group or a  $C_{1-3}$  alkoxy  $R^3$  indicates a hydrogen atom or a  $C_{1\cdot 3}$  alkyl group, and  $R^4$ ndicates a hydrogen atom, an optionally halogenated C<sub>1-3</sub> halogenated or may be substituted with a C<sub>1-3</sub> alkoxy group; group; R' indicates a C1-3 alkoxy group which may alkoxy group or a pyrrolyl group (for example, 1-, pyrrolyl group).

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In the formula (Ia), the compound wherein  $R^1$  is a  $C_{1-3}$ group; R3 is a hydrogen atom and R4 is a hydrogen atom or an optionally halogenated  $C_{1-3}$  alkoxy group is particularly  $R^2$  is an optionally halogenated  $C_{1-3}$  alkoxy alkyl group; 20

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preferred.

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σĘ substituents is 2 or more, each substituent groups may be optionally having a substituent group, a hydroxy group, an substituent group" of the "benzene ring optionally having example, a halogen atom, a nitro group, an alkyl group alkoxy group optionally having a substituentgroup, an aryl group, an aryloxy group, a carboxy group, an acyl group, an acyloxy group, a 5- to 10-membered heterocyclic group and The benzene ring may be substituted with about 1 In the compound represented by the above-mentioned referred to as Compound (I)), the substituent group" represented by ring A includes, for or different. Among these substituent groups, an alkoxy group optionally having number having the optionally substituent group and the like are preferred. to 3 of these substituent groups. When dnoxb. alkyl (hereinafter, an substituent group, atom, formula (=) the like. same halogen the

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The halogen atom includes fluorine, chlorine, bromine atom and the like. Among these, fluorine is preferred.

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of the "alkyl group optionally having a substituent of the "alkyl group optionally naving a substituent group", for example, a C<sub>1-</sub>, alkyl group heptyl As the "substituent butyl, (for example, a methyl, ethyl, propyl, isopropyl, tert-butyl, pentyl, hexyl, is exemplified. As the "alkyl group" isobutyl, sec-butyl, group and the like) group"

the number of these substituent groups may be about 1 group", for example, a halogen atom, a hydroxy group, a C<sub>1-6</sub> alkoxy group (for example, methoxy, ethoxy, propoxy, butoxy and the more, example, be exemplified, number of substituent group is 2 or each substituent groups may be the same or different. (for methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl dronb like), a carbamoyl group and the like can alkoxy-carbonyl a Cl-6 to 3. When the like), the

"alkoxy group group", and The "alkoxy group" of the "alkoxy group optionally having a substituent group" includes, for example, a  $C_{1-\delta}$ and the like) and optionally having a substituent group" are exemplified by of the propoxy, those for the above-mentioned "substituent group" ethoxy, the number of the substituent group is the same. a substituent the the like. The "substituent group" of pentoxy methoxy, having isopropoxy, butoxy, isobutoxy, example, "alkyl group optionally group (for alkoxy

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The "aryl group" include, for example, a C.14 aryl 2-naphthyl, biphenyl, 2-anthryl group and the like, and the like. a phenyl, 1-naphthyl, group (for example,

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C.6-14 aryloxy group (for example, a phenyloxy, 1-naphthyloxy, 2for example, naphthyloxy and the like) and the like. includes, The "aryloxy group"

includes, for example, a formyl, alkylcarbonyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, group" "acyl

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alkylsulfinyl, alkylsulfonyl group and the like.

group and C1-6 alkylexample, acetyl, propionyl æ includes, group" "alkylcarbonyl the like) and the like. carbonyl group (for

The "alkoxycarbonyl group" includes, for example, a ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl group and C. alkoxy-carbonyl group (for example, a methoxycarbonyl, the like) and the like.

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The "alkylcarbamoyl group" include, a N-C1-6 alkylcarbamoyl group (for example, N,N-dimethylcarbamoyl, N,N-N, N-diC<sub>1-6</sub> alkylmethylcarbamoyl, and the like. Ø sthylcarbamoyl group and the like), example, diethylcarbamoyl group and the like), (for dronb carbamoyl

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The "alkylsulfinyl group" includes, for example, a C1-7 ethylsulfinyl, propylsulfinyl, isoprocylsulfinyl group and methylsulfinyl, ιΩ example, (for the like) and the like. drozb alkylsulfinyl

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The "alkylsulfonyl group" includes, for example, a  $C_{1-1}$ and methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl group đ example, (for the like) and the like. alkylsulfonyl group

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the ם Ę alkoxycarbonyloxy group, alkylsulfinyloxy group, an alkylsulfonyloxy group and example, group, alkylcarbamoyloxy includes, for alkylcarbonyloxy group, an The "acyloxy group" an group, carbamoyioxy

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like.

propionyloxy The "alkylcarbonyloxy group" includes, a C1-6 alkylacetyloxy, example, group and the like) and the like. (for carbonyloxy group

The "alkoxycarbonyloxy group" includes, for example, a methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, outoxycarbonyloxy group and the like, and the like. (for dnoxb alkoxy-carbonyloxy ڙ.

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The "alkylcarbamoyloxy group" includes, a  $\mathbb{C}_{1-6}$  alkylmethylcarbamoyloxy, ethylcarbamoyloxy group and the like) and the like. example, (for carbamoyloxy group

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The "alkylsulfinyloxy group" includes, for example, a isopropylsulfinyloxy C1., alkylsulfinyloxy group (for example, methylsulfinyloxy, ethylsulfinyloxy, propylsulfinyloxy, group and the like) and the like. The "alkylsulfonyloxy group" includes, for example, a ethylsulfonyloxy, propylsulfonyloxy, isopropylsulfonyloxy  $C_{1-\gamma}$  alkylsulfonyloxy group (for example, methylsulfonyloxy, group and the like, and the like.

sulfur atom and an oxygen atom in addition to a carbon atom. to three) hetero atoms selected from a nitrogen atom, a The 5- to 10-membered heterocyclic group include, for 6-membered) neterocyclic group which contains one or more (for example, Specific example includes 2- or 3-thienyl group, example, a 5- to 10-membered (preferably 5- or

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or 5-Among these, 3or 3-pyrrolyl or 4-2-3-, 7, ลร 7 or 3-indolyl group. 2such 5- or 8-quinolyl group, 2- or 3-furyl group, 1-, or 6-membered heterocyclic groups pyrrolyl groups are preferred. isoquinolyl group, 1-, 2group, 2-, 3-, 4-, 1-pyridyl group,

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2 substituent groups selected from a halogen atom, an Aing A is preferably a benzene ring which may have 1 6-membered optionally an or group, 5 and  $C_{1-4}$  alkyl dronb C<sub>1-4</sub> alkoxy halogenated heterocyclic group. halogenated optionally

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In the above-mentioned formula (I'), the "aromatic isothiazole, imidazole, pyrazole, 1,2,3-oxadiazole, 1,2,4-1,2,4-triazole, tetrazole, pyridine, pyridazine, pyrimidine monocyclic represented by the "a pyridine ring optionally having a substituent group" are particularly preferred. The ring" 9 membered aromatic monocyclic heterocyclic rings such as oxadiazole, 1,3,4-oxadiazole, furazane, 1,2,3-thiadiazole, 1,2,3-triazole, "a benzene ring "optionally oxazole, isoxazole, thiazole, <u>ئ</u> 5 heterocyciic includes, for example, "aromatic the heterocyclic ring" represented by ring C', of 1,3,4-thiadiazole, may have a substituent group" monocyclic the ring" As ring A and pyrrole, triazine. heterocyclic represented by ring C' aromatic 1,2,4-thiadiazole, thiophene, above-mentioned and substituted monocyclic pyrazine

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represented by the above-mentioned ring A at substitutable to the exemplified with respect substituent substituent of t t ๙ ø have 'pyridine ring optionally having have may may substituent groups as those ပ် which ring benzene ring represented by positions. The position wherein "aromatic monocyclic heterocyclic ring" of the "aromatic monocyclic heterocyclic ring optionally having a substituent group" is condensed with an imidazole moiety is not specifically limited.

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optionally having a substituent group", and the number of οĘ the the above-mentioned "alkyl group the C,-16 aralky\_ group (for example, C,-10 arylC,-6 alkyl group of the "aralkyl group the substituent group is 2 or more, each substituent groups substituent group" represented by  $\mathbb{R}^0$  includes, for example, such as benzyl and phenethyl and the like. of the "aralkyl group optionally having the number Ή) 0 11. the include or respect the substituent groups is 1 to about 4. When above-mentioned formula (I') optionally having a substituent group" with Examples of the "substituent group" exemplified be the same or different. of substituent group" those aralkyl group" the as groups

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The "acyl group" represented by  $R^{\rm o}$  includes, for example, the "acyl group" described as the substituent

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group of the above-mentioned ring A.

The "acyloxy group" represented by  $R^0$  includes, for example, the "acyloxy group" described as the substituent group of the above-mentioned  $r\dot{=}ng~A.$ 

The preferable  $\mathbb{R}^0$  is a hydrogen atom.

In the above-mentioned formula (I') or (I), the "alkyl group optionally having a substituent group" represented by  $R^1$ ,  $R^2$  or  $R^3$  includes the "alkyl group optionally having a substituent group" described as the substituent group of the above-mentioned ring  $\lambda$ .

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The "alkoxy group optionally having a substituent group" represented by  $R^1$ ,  $R^2$  or  $R^3$  includes the "alkoxy group optionally having a substituent group" described as the substituent group of the above-mentioned ring A.

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The "amino group optionally having a substituent group" represented by R¹,  $R^2$  or  $R^3$  includes, for example, an amino group, a mono- $C_{L-6}$  alkylamino group (for example, a mono- $C_{6-14}$  arylamino group (for example, phenylamino, 1-naphthylamino, 2-naphthylamino and the like), a di- $C_{L-6}$  alkylamino group (for example, dimethylamino, diethylamino and the like), a di- $C_{L-14}$  arylamino group (for example, diphenylamino and the like), a the like) and the like.

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The preferable  $\mathbb{R}^1$  is a  $C_{1-6}$  alkyl group, a  $C_{1-6}$  alkoxy- $C_{1-6}$  alkoxy group and a di- $C_{1-6}$ 

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alkylamino group. Further preferable  $R^2$  is a  $C_{1-3}$  alkyl group or a  $C_{1-3}$  alkoxy group.

The preferable  $R^2$  is a hydrogen atom, a  $C_{1-\delta}$  alkoxy- $C_{1-\delta}$  alkoxy group or an optionally halogenated  $C_{1-\delta}$  alkoxy group. Further preferable  $R^3$  is a  $C_{1-3}$  alkoxy group which may be optionally halogenated or may be optionally substituted with a  $C_{1-3}$  alkoxy group.

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The preferable  $R^3$  is a hydrogen atom or a  $C_{1-6}$  alkyl group. Further preferable  $R^3$  is a hydrogen atom or a  $C_{1-3}$  alkyl group (in particular, a hydrogen atom).

The preferable Y is a nitrogen atom.

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As the specific example of the compound (I), the following compounds are exemplified.

2-[[[3-methy1-4-(2,2,2-trifluoroethoxy)-2-

pyridinyl]methyl]sulfinyl]-lH-benzimidazole (lansoprazole),
2-[[(3,5-dimethyl-4-methoxy-2-pyridinyl)methyl]sulfinyl]-5methoxy-lH-benzimidazole,

2-[[[4-(3-methoxypropoxy)-3-methyl-2-

pyridinyl]methyl]sulfinyl]-lH-benzimidazole sodium salt,

20 5-difluoromethoxy-2-[[(3,4-dimethoxy-2-

Among these compounds, lansoprazole, namely 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-

oyridinyl)methyl]sulfinyl]-lH-benzimidazole and the like.

pyridinyl]methyl]sulfinyl]-1H-benzimidazole is preferable

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the the ٦. The present invention is preferably applied to the imidazopyridine compound in addition to the PPI of tenatoprazole above-mentioned benzimidazole compound. As the PPI of examble, ioi imidazopyridine compound, exemplified. οĘ

Further, the above-mentioned compound (I) and compound For example, the optically active compounds such as optically active compound of lansoprazole, that is, (R)-2-(I') including the imidazopyridine compound may be racemic, R-isomer and and optically active compounds such as [[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-

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pyridinyl]methyl]sulfinyl]-lH-benzimidazole and (S)-2-[[[3methyl-4-(2,2,2-trifluoroethoxy)-2-

for arc being pyridinyl]methyl]sulfinyl]-1H-benzimidazole are preferable preparation itself as described later and stabilized by compounding a basic inorganic salt and ŝ lansoprazole, lansoprazole R-isomer and lansoprazole but since they the present invention in particular. Further, further providing an intermediate layer, those amorphous as well as crystalline can be also used. crystals are usually preferred, stabilized by for

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÷, for example, a salt with an inorganic base, a salt with an organic base, a salt with a basic amino acid and the like (I) and preferably a pharmacologically acceptable salt, (I') and compound compound of salt

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are mentioned.

salt and calcium The preferable salt with an inorganic base includes, salt and magnesium salt; ammonium salt and the like. as sodium potassium salt; alkali earth metal salts such such as salts alkali metal example,

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neterocyclic amine (pyridine, picoline and the like), an the preferable example of the salt with an organic alkanolamine (ethanolamine, diethanolamine, triethanolamine with an alkylamine like), dicyclohexylamine, the and salts dibenzylethylenediamine and the like. triethylamine for example, like), (trimethylamine, base includes, the and

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The preferable example of the salt with a basic amino acid includes, for example, salts with arginine, lysine, ornithine and the like.

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earth metal salt are preferred. A sodium salt is preferred Among these salts, an alkali metal salt and an alkali particularly. The compound (I') or (I) can be produced by known 98/21201, JP-A 52-62275, JP-A 54-141783 and the like, or analogous methods thereto. Further, the optically active compound (I) can be obtained by optical resolution methods JP-A 61-50978, USP 4628098, JP-A 10-195068, disclosed in, methods and are produced by example, methods,

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fractional recrystallization method, a chiral

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method, a diastereomer method, a method using microorganism or enzyme, and the like) and an asymmetric oxidation method, etc. Further, lansoprazole R-isomer can be produced according to production methods described in, for example, WO 00-78745, WO 01/83473 and the like.

. س The benzimidazole compound having antitumor activity used in the present invention is preferably lansoprazole, omeprazole, rabeprazole, pantoprazole, leminoprazole, tenatoprazole (TU-199) and the like, or optically active compounds thereof and pharmacologically acceptable salts thereof. Lansoprazole or an optically active compound thereof, in particular R-isomer is preferred. Lansoprazole or an optically active compound thereof, in particular R-isomer is preferably in a form of crystal, but may be an amorphous form. Further, they are also suitably applied to the prodrug of these PPIs.

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Examples of these preferable prodrugs include the compound represented by the following general formula (II) and (III) in addition to the prodrug which is included in compound (I) or (I').

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In the compound represented by the above formula (II) hereinafter, referred to as compound (II)), ring B

designates a "pyridine ring optionally having substituents"

substituted by alkyl group having 1 to 6 carbon atoms, such propyl group etc., and the like), an amino group optionally acylamino group such as formamide, acetamide etc., and the like), a lower alkoxy group optionally having substituents naving substituents (e.g., amino; amino group mono- or dioptionally having substituents (e.g., alkyl group having naving substituents" represented by ring B may have 1 to substituent, for example, a halogen atom (e.g., fluorine, substituents at substitutable positions thereof. As the as methylamino, dimethylamino, ethylamino, diethylamino ď The pyridine ring of the "pyridine ring optionally to 6 carbon atoms such as methyl group, ethyl group, (e.g., alkoxy group having 1 to 6 carbon atoms such chlorine, bromine, iodine etc.), a hydrocarbon group group etc., and the like), an amide group (e.g., C<sub>1-3</sub>

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methoxy, ethoxy, 2,2,2-trifluoroethoxy, 3-methoxypropoxy group and the like), a lower alkylenedioxy group (e.g.,  $C_{1-3}$  alkylenedioxy group such as methylenedioxy, ethylenedioxy etc., and the like) and the like can be mentioned.

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thiol group, a carboxyl group, a lower alkanoyl group (e.g., group (e.g., alkyl group having 1 to 6 carbon atoms such as propionyl, butyryl group and the like), a lower alkanoyloxy the like), a lower alkoxy group (e.g., alkoxy group having group (e.g., formyloxy; C1-C6 alkyl-carbonyloxy group, such pyridine ring optionally having substituents" represented ethynyl, propargyl group and the like), a cycloalkyl group (e.g., cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl group and methyl, ethyl, propyl group and the like), a lower alkenyl group (e.g., alkenyl group having 2 to 6 carbon atoms such as vinyl, allyl group and the like), a lower alkynyl group 1 to 6 carbon atoms such as methoxy, ethoxy group and the fluorine, chlorine, bromine, iodine etc.), a lower alkyl As the substituent, which is the substituent of the like), a nitro group, a cyano group, a hydroxy group, a as acetyloxy, propionyloxy group and the like), a lower alkoxycarbonyl group (e.g., C1-C, alkoxy-carbonyl group, by ring B can have, for example, a halogen atom (e.g., (e.g., alkynyl group having 2 to 6 carbon atoms such formyl; C1-C, alkyl-carbonyl group, such as acetyl,

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dimethyicarbamoyl group etc., and the like), an amino group mono- or di-substituted by alkyl group having 1 to 6 carbon liethylamino group etc., and the like) and the like, can be parbamoyl; carbamoyl group mono- or di-substituted by alkyl group and the like), an aryl group (e.g., aryl group having 6 to 14 carbon atoms such as phenyl, naphthyl group and the like), an aryloxy group (e.g., aryloxy group having 6 to 14 group and the like), an aralkyloxycarbonyl group (e.g., C,group having 1 to 6 carbon atoms, such as methylcarbamoyl, position of the substitution are not particularly limited. arylcarbonyloxy group (e.g., C.-C., aryl-carbonyloxy group, carbon atoms such as phenyloxy, naphthyloxy group and the group, such as benzoyl, naphthoyl group and the like), an optionally having substituents (e.g., amino; amino group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl such as benzoyloxy, naphthoyloxy group and the like), a  $c_{11}$  aralkyloxy-carbonyl group, such as benzyloxycarbonyl like), an arylcarbonyl group (e.g.,  $C_6-C_1$ , aryl-carbonyl stoms, such as methylamino, dimethylamino, ethylamino, mentioned, wherein the number of substituents and the carbamoy' group optionally having substituents (e.g.,

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While the number of substituents and the position of substitution of the "pyridine ring optionally having substituents" represented by ring B are not particularly limited, 1 to 3 substituents mentioned above preferably

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substitute any of the 3-, 4- and 5-positions of the pyridine ring.

As the "pyridine ring optionally having substituents" represented by ring B, 3-methyl-4-(2,2,2-trifluoroethoxy)-

2-pyridyl is preferable.

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In the present invention, ring C represents a "benzene ring optionally having substituents" or an "aromatic monocyclic heterocycle optionally having substituents", which is condensed with an imidazole part. Of these, the former is preferable.

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substituents (e.g., alkoxy group having 1 to 6 carbon atoms mono- or di-substituted by alkyl group having 1 to 6 carbon etc., and the like), a lower alkoxy group optionally having optionally having substituents (e.g., alkyl group having l to 6 carbon atoms selected from methyl group, ethyl group, substituent, for example, a halogen atom (e.g., fluorine, having substituents" represented by ring C may have 1 to optionally having substituents (e.g., amino; amino group the (e.g.,  $C_{1-3}$  acylamino group such as formamide, acetamide diethylamino group etc., and the like), an amide group such as methylamino, dimethylamino, ethylamino, The benzene ring of the "benzene ring optionally As chlorine, bromine, iodine etc.), a hydrocarbon group n-propyl group etc., and the like), an amino group substituents at substitutable positions thereof. atoms,

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such as methoxy, ethoxy, difluoromethoxy group etc., and the like), a lower alkylenedioxy group (e.g.,  $C_{1\cdot 3}$  alkylenedioxy group such as methylenedioxy, othylenedioxy etc., and the like), and the like can be mentioned.

group (e.g., alkyl group having 1 to 6 carbon atoms such as thiol group, a carboxyl group, a lower alkanoyl group (e.g., methyl, ethyl, propyl group and the like), a lower alkenyl group (e.g., alkenyl group having 2 to 6 carbon atoms such as vinyl, allyl group and the like), a lower alkynyl group ethynyl, propargyl group and the like), a cycloalkyl group (e.g., cycloalkyl group having 3 to 8 carbon atoms such as cyclopentyl, cyclohexyl group and the like), a lower alkoxy group. (e.g., alkoxy group having benzene ring optionally having substituents" represented to 6 carbon atoms such as methoxy, ethoxy group and the As the substituent, which is the substituent of the fluorine, chlorine, bromine, iodine etc.), a lower alkyl (e.g., alkynyl group having 2 to 6 carbon atoms such as like), a nitro group, a cyano group, a hydroxy group, a by ring C can have, for example, a halogen atom (e.g., cyclopropyl, cyclobutyl, ц 2 15 20

formyl; C<sub>1-6</sub> alkyl-carbonyl group, such as acetyl, propionyl, butyryl group and the like), a lower alkanoyloxy group (e.g., formyloxy; C<sub>1-6</sub> alkyl-carbonyloxy group, such as acetyloxy, propionyloxy group and the like), a lower alkoxycarbonyl group (e.g., C<sub>1-6</sub> alkoxy-carbonyl group, such

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like), an aryloxy group (e.g., aryloxy group having 6 to 14 dimethylcarbamoyl group etc., and the like), an amino group carbamoyl; carbamoyl group mono- or di-substituted by alkyl mono- or di-substituted by alkyl group having 1 to 6 carbon aralkyloxy-carbonyl group, such as benzyloxycarbonyl group and the like), an aryl group (e.g., aryl group having 6 to diethylamino group etc., and the like) and the like can be as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl group position of the substitution are not particularly limited. carbon atoms such as phenyloxy, naphthyloxy group and the group, such as benzoyl, naphthoyl group and the like), an group having 1 to 6 carbon atoms such as methylcarbamoyl, optionally having substituents (e.g., amino; amino group arylcarbonyloxy group (e.g., C., aryl-carbonyloxy group, 14 carbor atoms such as phenyl, naphthyl group and the and the like), an aralkyloxycarbonyl group (e.g., C,-1, like), an amylcarbonyl group (e.g., C<sub>6-14</sub> aryl-carbonyl such as benzoyloxy, naphthoyloxy group and the like), carbamoyl group optionally having substituents (e.g., mentioned, wherein the number of substituents and the atoms such as methylamino, dimethylamino, ethylamino,

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As the "benzene ring optionally having substituents" represented by ring C, a benzene ring is preferable.

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As the "aromatic monocyclic heterocycle" of the "aromatic monocyclic heterocycle optionally having

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itiiante" ranrasantad hy ring C for example. A 5-

substituents" represented by ring C, for example, a 5- or 5-membered aromatic monocyclic heterocycle such as furan,

thiophene, pyrrole, oxazole, isoxazole, thiazole,

isothiazole, imidazole, pyrazole, 1,2,3-oxadiazole, 1,2,4-5 oxadiazole, 1,3,4-oxadiazole, furazan, 1,2,3-thiadiazole,

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1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole,

1,2,4-triazole, tetraxole, jyridine, pyridazine, pyrimidine, pyrazine, triazine etc., and the like can be mentioned. As the "aromatic monocyclic heterocycle" represented by ring C,

a pyridine ring is particularly preferable. It may have, at substitutable positions thereof, 1 to 4 substituents similar to those for the "benzene ring optionally having substituents" represented by ring C.

The position where the "aromatic monocyclic

heterocycle" of the "aromatic monocyclic heterocycle optionally having substituents" is condensed with the imidazole part is not particularly limited.

In the present invention,  $X_1$  and  $X_2$  represent an oxygen atom and a sulfur atom, respectively. Both  $X_1$  and

20 X; preferably represent an oxygen atom.

In the present invention, W represents a "divalent chain hydrocarbon group optionally having substituents", or the formula:

 $--W_1-Z-W_2-$ 

25 wherein W<sub>1</sub> and W<sub>2</sub> are each a "divalent chain hydrocarbon

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an arylsulfonyl group optionally having substituents, a heterocyclic group an aralkyloxycarbonyl group, a naving substituents", an oxygen atom,  $50_n$  wherein n is 0, thiocarbamoyl group, a lower alkylsulfinyl group, a lower an optionally having substituents, when  ${\tt Z}$  is an oxyger atom, substituents", a "divalent heterocyclic group optionally or 2 or >N-E wherein E is a hydrogen atom, a hydrocarbon optionally having substituents, a lower alkanoyl group, alkylsulfamoyl group, a di-lower alkylsulfamoyl group, or a bond, and 2 is a divalent group such as alkylsulfonyl group, a sulfamoyl group, a mono-lower Particularly, W is preferably a "divalent chain hydrocarbon group optionally having 'divalent hydrocarbon ring group optionally having an arylcarbonyl group, or a carbamoyl group 50, or >N-E, W, and W, are each a "divalent chain arylsulfamoyl group, an arylsulfinyl group, lower alkoxycarbonyl group, nydrocarbon group". substituents" group"

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As the "divalent chain hydrocarbon group" of the "divalent chain hydrocarbon group optionally having substituents" represented by W and "divalent chain hydrocarbon group" represented by W, and W, for example, a  $C_{1-6}$  alkylene group (e.g., methylene, ethylene, trimethylene etc.), a  $C_{2-6}$  alkenylene group (e.g., ethenylene etc.), a  $C_{2-6}$  alkynylene group (e.g., ethynylene etc.) and the like can

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be mentioned. The divalent chain hydrocarbon group for W may have 1 to 6 substituents similar to those for the "benzene ring optionally having substituents" represented by ring C at substitutable positions thereof.

- the "divalent chain hydrocarbon group" represented by W, is ethylene group is particularly preferable. When Z is an oxygen atom, SO, or >N-E (n and E are as defined above), a methylene preferably a hydrocarbon group having 2 or more carbon W, an of the divalent chain hydrocarbon group optionally having substituents" represented by W and "divalent chain As As the "divalent chain hydrocarbon group" group and an ethylene group are preferable. hydrocarbon group" represented by W, and W2, atoms. Ŋ 10
- ring group optionally having substituents" represented by 2,

  for example, an alicyclic hydrocarbon ring, an aromatic
  hydrocarbon ring and the like can be mentioned, with
  preference given to one having 3 to 16 carbon atoms, which
  may have 1 to 4 substituents similar to those for the
  "benzene ring optionally having substituents" represented
  by ring C at substitutable positions thereof. As the
  hydrocarbon ring, for example, cycloalkane, cycloalkene,
  arene and the like are used.
- As a cycloalkane in the "divalent hydrocarbon ring

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example, a lower cycloalkane and the like are preferable, and, for example, C<sub>2-10</sub> cycloalkane such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclobctane, bicyclo[2.2.1]heptane, adamantane etc., and the like are generally used.

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As a cycloalkene in the "divalent hydrocarbon ring group optionally having substituents" represented by 2, for example, a lower cycloalkene is preferable, and, for example, C<sub>4.9</sub> cycloalkene such as cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene, cyclooctene etc., and the like are generally used.

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As an arene in the "divalent hydrocarbon ring group optionally having substituents" represented by Z, for example, a C<sub>6-14</sub> arene such as benzene, naphthalene, phenanthrene etc., and the like are preferable, and, for example, phenylene and the like are generally used.

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As a heterocycle in the "divalent heterocyclic group optionally having substituents" represented by Z, ā 5- to 12-membered "aromatic heterocycle" or "saturated or unsaturated non-aromatic heterocycle" containing, as ring-constituting atom (ring atom), 1 to 3 (preferably 1 or 2) kinds of at least 1 (preferably 1 to 4, more preferably 1 or 2) hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom etc., and the like can be mentioned,

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which may have 1 to 4 substituents similar to those for the "benzene ring optionally having substituents" represented by ring C at substitutable positions thereof.

As an aromatic heterocycle in the "divalent heterocyclic group optionally having substituents" represented by Z, an aromatic monocyclic heterocycle, an aromatic fused heterocycle and the like can be mentioned.

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As the "aromatic monocyclic heterocycle", for example, a 5- or 6-membered aromatic monocyclic heterocycle such as furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, isothiazole, imidazole, pyrazole, 1,2,3-oxadiazole, 1,2,4-coxadiazole, 1,3,4-oxadiazole, furazan, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, pyridine, pyridine, pyridine, pyriazole, tetrazole, pyridine, pyridizole, triazine etc., and the like can be mentioned.

As the "aromatic fused heterocycle", for example, a 8to 12-membered aromatic fused heterocycle such as
benzofuran, isobenzofuran, benzothlophene,
isobenzothlophene, indole, isoindole, IH-indazole,

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benzimidazole, benzoxazole, 1,2-benzisoxazole, benzothiazole, 1,2-benzisozhiazole, 1H-benzotriazole, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, naphthyridine, purine, pteridine, carbazole, carboline, acridine, phenoxazine, phenothiazine, phenazine, phenoxathiin, thianthrene, phenanthridine,

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1,2,4-triazolo[4,3-b]pyridazine etc., and the like can be imidazo[1,2-a]pyrimidine, 1,2,4-triazolo[4,3-a]pyridine, phenanthroline, indolizine, pyrrolo[1,2-b]pyridazine, imidazo[1,2-b]pyridazine, pyrazolo[1,5-a]pyridine, imidazo[1,2-a]pyridine, imidazo[1,5-a]pyridine, mentioned.

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(aliphatic heterocycle) such as oxylane, azetidine, oxetane, thietane, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, unsaturated (preferably saturated) non-aromatic heterocycle As a saturated or unsaturated non-aromatic heterocycle 8 in the "divalent heterocyclic group optionally having substituents" represented by Z, for example, a 3- to membered (preferably 5- or 6-membered) saturated or piperidine, tetrahydropyran, tetrahydrothiopyran,

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These may be oxo-substituted and may be, for example, oxotetrahydropyran, 2-oxotetrahydrothiophene, 2-oxothiane, oxothiepane, 2-oxothiazepane, 2-oxooxocane, 2-oxothiocane, 2-2-oxoazetidine, 2-oxopyrrolidine, 2-oxopiperidine, <del>'</del>2 oxazepane, 2-oxazocane, 2-oxotetrahydrofuran, 2-2-oxopiperazine, 2-oxooxepane, 2-oxooxazepane, 2-oxooxazocane, 2-oxothiazocane and the like.

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oxazocane, thiazocane etc., and the like can be mentioned.

thiene, oxazepane, thiazepane, azocane, oxocane, thiocane,

morpholine, thiomorpholine, piperazine, azepane, oxepane,

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of the The two bonds from the "hydrocarbon ring group"

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substituents" or the "heterocyclic group" of the "divalent represented by Z may be present at any possible position. divalent hydrocarbon ring group optionally having heterocyclic group optionally having substituents"

The "hydrocarbon group optionally having substituents" and "heterocyclic group optionally having substituents" represented by E is as defined in the following.

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example, formyl, a C1-6 alkyl-carbonyl group such as acetyl, for propionyl, butyryl, isobutyryl etc., and the like car be As the "lower alkanoyl group" represented by E, used.

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As the "lower alkoxycarbony' group" represented by E, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, for example, a  $C_{1-6}$  alkoxy-carbonyl group such butoxycarbonyl etc., and the like are used.

for the "aralkyloxycarbonyl" represented by E, example, a C,\_11 aralkyloxy-carbonyl group such as benzyloxycarbonyl etc., and the like are used. As

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As the "lower alkylsulfinyl group" represented by E, for example, a  $C_{1-6}$  alkylsulfinyl group such as

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methylsulfinyl, ethylsulfinyl etc., and the like are used. methylsulfonyl, ethylsulfonyl etc., and the like are used. 回 As the "lower alkylsulfonyl group" represented by for example, a  $C_{1-6}$  alkylsulfonyl group such as

the "mono-lower alkylsulfamoyl group" represented AS

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methylsulfamoyl, ethylsulfamoyl etc., and the like are used. by E, for example, a mono- $C_{1-\delta}$  alkylsulfamoyl group such as

dimethylsulfamoyl, diethylsulfamoyl etc., and the like are the "di-lower alkylsulfamoyl group" represented by for example, a  $\text{di-}C_{1-\delta}$  alkylsulfamoyl group such as used.

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example, a C<sub>6-:0</sub> arylsulfamoyl group such as phenylsulfamoyl, As the "arylsulfamoyl group" represented by E, for naphthylsulfamoyl etc., and the like are used.

example, a C<sub>6-10</sub> arylsulfinyl group such as phenylsulfinyl, As the "arylsulfinyl group" represented by E, for naphthylsulfinyl etc., and the like are used.

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example, a  $\mathsf{C}_{\mathsf{6-10}}$  arylsulfonyl group such as phenylsulfonyl, for represented by E, naphthylsulfonyl etc., and the like are used. As the "arylsulfonyl group"

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for As the "arylcarbonyl group" represented by E, example,  $C_{6-10}$  aryl-carbonyl group such as benzoyl, naphthoyl etc., and the like are used.

heterocyclic group optionally having substituents, and in The "carbamoyl group optionally having substituents" represented by E is, for example, a group of the formula R<sub>2</sub> and R<sub>3</sub> may form a ring together hydrocarbon group optionally having substituents or a CONR,R, wherein R, and R, are each a hydrogen atom, a with the adjacent nitrogen atom, and the like. the formula -CONR<sub>2</sub>R<sub>3</sub>,

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substituents is preferable and a lower  $(C_{1-\delta})$  alkyl group is particularly preferable. The "hydrocarbon group optionally represented by R are as defined in the optionally having substituents", and R can be bonded to W. following. A detailed explanation of the case where R is In the present invention, R is a "hydrocarbon group optionally having substituents" or a "heterocyclic group having substituents" and "heterocyciic group optionally Of these, a  $C_{1-\varepsilon}$  hydrocarbon group optionally having bonded to W is given in the following. having substituents"

Among others, each of  $\mathbb{D}_1$  and  $\mathbb{D}_2$  is preferably a bond an oxygen atom, a sulfur atom or  $> NR_1$ , and in the formula, or an oxygen atom, and particularly preferably,  $D_{\rm i}$  is an In the present invention,  $\mathbf{D}_1$  and  $\mathbf{D}_2$  are each a bond,  $R_{\rm l}$  is a hydrogen atom or a hydrocarbon group optionally excludes a case where  $D_1$  and  $D_2$  are both respectively a having substituents. However, the present invention The hydrocarbon group optionally having substituents" represented by  $R_1$  is as defined in the following. oxygen atom and  $D_{\scriptscriptstyle 2}$  is an oxygen atom or a bond. bond.

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saturated heterocyclic group optionally having substituents, drozb In the present invention, G is a "hydrocarbon group hydrocarbon group optionally having substituents or or a "heterocyclic optionally having substituents". Of these, a  $C_{1\cdot\epsilon}$ optionally having substituents"

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which contains, as ring-constituting atom, 1 to 4 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom is preferable. As G, among others, a C<sub>1-6</sub> hydrocarbon group optionally having substituents or a saturated oxygencontaining heterocyclic group optionally having substituents, which further contains, as ring-constituting atom, 1 to 3 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom is preferable. The "hydrocarbon group optionally having substituents" and "heterocyclic group optionally having substituents" represented by G are as defined in the following.

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As the "hydrocarbon group" of the "hydrocarbon group optionally having substituents" represented by the abovementioned E, R, R, and G, for example, a saturated or unsaturated aliphatic hydrocarbon group, a saturated or unsaturated alicyclic hydrocarbon group, a saturated or aromatic hydrocarbon group, an aromatic-saturated or unsaturated alicyclic hydrocarbon group and the like can be mentioned, with preference given to those having 1 to 16, more preferably 1 to 6, carbon atoms. Specific examples thereof include alkyl group, alkenyl group, alkynyl group, cycloalkyl group, aryl group, cycloalkylalkyl group, cycloalkylalkyl group, aryl group and arylalkyl group and

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For example, the "alkyl group" is preferably a lower alkyl group (C<sub>1-6</sub> alkyl group) and the like, and, for example, a C<sub>1-6</sub> alkyl group such as mcthyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 1-ethylpropyl, hexyl etc., and the like are generally used. For R, a lower alkyl group (C<sub>1-6</sub> alkyl group) is preferable, particularly a methyl group is preferable.

For example, the "alkenyl group" is preferably a lower alkenyl group and the like, and, for example, a C<sub>2</sub>., alkenyl group such as vinyl, 1-propenyl, allyl, isopropenyl, butenyl, isobutenyl, 2,2-dimethyl-pent-4-enyl etc., and the like are generally used.

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For example, the "alkynyl group" is preferably a lower alkynyl group and the like, and, for example, a C<sub>2-6</sub> alkynyl group such as ethynyl, propargyl, 1-propynyl etc., and the like are generally used.

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For example, the "cycloalkyl group" is preferably a lower cycloalkyl group and the like, and, for example, a C<sub>3-10</sub> cycloalkyl group such as cyclopropyl, cyclobutyl, cyclohetyl, cyclohetyl, cyclohetyl, bicyclo[2.2.1]heptanyl and adamantyl etc., and the like are generally used.

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For example, the "cycloalkenyl group" is preferably a lower cycloalkenyl group, and, for example, a  $C_{3-10}$ 

cycloalkenyl group such as cyclopropenyl, cyclobutenyl,

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the like.

cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, bicyclo[2.2.1]hept-5-en-2-yl etc., and the like are gencrally used.

For example, the "cycloalkylalkyl group" is preferably a lower cycloalkylalkyl group, and, for example, a C<sub>4-9</sub> cycloalkylalkyl group such as cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclobexylethyl, cyclobexylethyl etc., and the like are generally used.

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preferably a lower cycloalkenylalkyl group" is preferably a lower cycloalkenylalkyl group, and, for example, C<sub>t-9</sub> cycloalkenylalkyl such as cyclopentenylmethyl, cyclohexenylethyl, cyclohexenylpropyl, cycloheptenylmethyl, cycloheptenylethyl and bicyclo[2.2.1]hept-5-en-2-ylmethyl etc., and the like are generally used.

For example, the "aryl group" is preferably a C<sub>5-14</sub> aryl group such as phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-anthryl etc., and the like, and, for example, phenyl group and the like are generally used.

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The "arylalkyl group" contains, as the aryl moiety, the "aryl group" defined above, and as the alkyl moiety, the "alkyl group" defined above. Of these, for example, a  $C_{6-14}$  aryl- $C_{1-6}$  alkyl group is preferable, and, for example, benzyl, phenethyl and the like are generally used.

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amidino group, an imino group, an alkylenedioxy group (e.g., and the like), an optionally halogenated lower alkoxy group of the alkyl group (e.g., C<sub>1-6</sub> alkyl such as methyl, ethyl, propyl, as chloromethyloxy, dichloromethyloxy, trichloromethyloxy, fluoromethyloxy, difluoromethyloxy, trifluoromethyloxy, 2and G may have, lsopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, (e.g., a mono-, di- or tri-halogeno-C<sub>i-6</sub> alkoxy group such group, a phosphono group, an optionally halogenated lower (e.g.,  $C_{1-6}$  alkoxy group such as methoxy, ethoxy, propoxy, sopropoxy, butoxy, isobutoxy, pentyloxy, hexyloxy etc., ethylenedioxy etc., and the like), a lower alkoxy group crifiuoroethyl, pentafluoroethyl, 3,3,3-trifluoropropyl, hydroxy group, a thiol group, a sulfo group, a sulphino 1-ethylpropyl, hexyl and the like, a mono-, d1- or tr1for example, a halogen atom (c.g., fluorine, chlorine, difluoromethyl, trifluoromethyl, 2-bromoethyl, 2,2,2-As the substituent that the "hydrocarbon group" trifluorohexyl etc., and the like), an oxo group, an bromine, iodine etc.), a nitro group, a cyano group, 4,4,4-trifluorobutyl, 5,5,5-trifluoropentyl, 6,6,6-"hydrocarbon group optionally having substituents" C1-3 alkylenedioxy group such as methylenedioxy, dichloromethyl, trichloromethyl, fluoromethyl, nalogeno-C<sub>1-6</sub> alkyl group such as chloromethyl, ᅈ represented by the above-mentioned E, R, 15 25 20 ഗ 10

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20 15 ដ oromoethyloxy, 2,2,2-trifluoroethyloxy, pentafluoroethyloxy, propionyl, butyryl, isobutyryl etc., and the like), a lower like), a lower alkylthio group (e.g., a  $C_{1-\epsilon}$  alkylthio group alkanoyloxy group (e.g., formyloxy; a  $C_{1-6}$  alkyl-carbonyloxy the like), a carboxyl group, a lower alkanoyl group (e.g., alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl 3,3,3-trifluoropropyloxy, 4,4,4-trifluorobutyloxy, 5,5,5trifluoropentyloxy, 6,6,6-trifluorohexyloxy etc., and the isobutyryloxy etc., and the like), a lower alkoxycarbonyl such as methylthic, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, hexylthio etc., and etc., and the like), a lower alkylsulfonyl group (e.g., butoxycarbonyl etc., and the like), aralkyloxycarbonyl benzyloxycarbonyl etc., and the like), a thiocarbamoyl ethylsulfonyl etc., and the like), a sulfamoyl group, group (e.g., a C,\_11 aralkyloxy-carbonyl group such as group such as acetyloxy, propionyloxy, butyryloxy, formy:, a  $C_{1-6}$  alkyl-carbonyl group such as acetyl, mono-lower alkylsulfamoyl group (e.g., a mono-C<sub>1-6</sub> methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, group (e.g., a  $C_{1-\epsilon}$  alkoxy-carbonyl group such as group, a lower alkylsulfinyl group (e.g., a C<sub>1-6</sub> C1.6 alkylsulfonyl group such as methylsulfonyl alkylsulfamoyl group such as methylsulfamoyl,

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ethylsulfamoyl etc., and the like), di-lower alkylsulfamoyl

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optionally halogenated lower alkylcarbonylamino group (e.g., each a hydrogen atom, a hydrocarbon group optionally having substituents and in the formula -CONR,R,, R, and R, may form diethylsulfamoyl etc., and the like), an (e.g., a group of the formula -CONR,  $R_3$  wherein  $R_2$  and  $R_3$  are arylsulfinyl group (e.g., a C<sub>6-10</sub> arylsulfinyl group such as arylsulfonyl group (e.g., a C6-10 arylsulfonyl group such as naphthyl etc., and the like), an aryloxy group (e.g., a C<sub>6</sub>. as phenylsulfamoyl, naphthylsulfamoyl etc., and the like), arylcarbonyloxy group (e.g., a C<sub>r-10</sub> aryl-carbonyloxy group (e.g., a  $C_{\text{\tiny 6-10}}$  arylsulfamoyl group such the like), an arylthic group (e.g., a  $C_{\text{e-}10}$  arylthic group arylcarbonyl group (e.g., a C<sub>6-10</sub> aryl-carbonyl group such such as benzoyloxy, naphthoyloxy etc., and the like), an and such as phenylthio, naphthylthio etc., and the like), an phenylsulfiryl, naphthylsulfinyl etc., and the like), an ohery\_sulfonyl, naphthylsulfonyl etc., and the like), an like), a carbamoyl group optionally having substituents and the optionally halogenated C1-6 alkyl-carbonylamino group substituents or a neterocyclic group optionally having an aryl group (e.g., a C<sub>6-10</sub> aryl group such as phenyl, 10 aryloxy group such as phenyloxy, naphthyloxy etc., group (e.g., a di-C<sub>1-6</sub> alkylsulfamoyl group such as such as acetylamino, trifluoroacetylamino etc., as benzoyl, naphthoyl etc., and the like), an arylsulfamoyl group dimethylsulfamoyl, 25

a ring together with the adjacent nitrogen atom), an amino group optionally having substituents (e.g., a group of the formula -NR<sub>2</sub>R<sub>3</sub>, Wherein R, and R<sub>3</sub> are as defined above and in the formula -NR<sub>2</sub>R<sub>3</sub>, R<sub>2</sub> and R<sub>3</sub> may form a ring\*together with the adjacent nitrogen atom), a ureido group optionally having substituents (e.g., a group of the formula -NHCONR<sub>2</sub>R<sub>3</sub>, Wherein R<sub>2</sub> and R<sub>3</sub> may form a ring together with the adjacent nitrogen atom), a carboxamide group optionally having substituents (e.g., a group of the formula -NR<sub>2</sub>COR<sub>3</sub>, wherein R<sub>2</sub> and R<sub>3</sub> are as defined above), a sulfonamice group optionally having substituents (e.g., a group of the formula -NR<sub>2</sub>SO<sub>2</sub>R<sub>3</sub>, wherein R<sub>2</sub> and R<sub>3</sub> are as defined above), a heterocyclic group optionally having substituents (as

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As the "hydrocarbon group" of the "hydrocarbon group optionally having substituents" for R<sub>2</sub> and R<sub>3</sub>, for example, a lower alkyl group (e.g., alkyl group having 1 to 6 carbon atoms such as methyl, ethy-, propyl group and the like), a lower alkenyl group (e.g., alkenyl group having 2 to 6 carbon atoms such as vinyl, allyl group and the like), a lower alkynyl group (e.g., alkynyl group having 2 to 6 carbon atoms such as ethynyl, propargyl group and the like), a gycloalkyl group (e.g., cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl,

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defined for R, and R, and the like are used.

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cyclopentenylmethyl, cyclohexenylmethyl group and the like), C, alkyl group, such as cyclopropylmethyl, cyclobutylmethyl, an aryl group (e.g., aryl group having 6 to 14 carbon atoms syclohexyl group and the like), a cycloalkenyl group (e.g., like), a cycloalkylalkyl group (e.g., C3-C9 cycloalkyl - C1group (e.g., C<sub>6</sub>-C<sub>14</sub> aryl - C<sub>1</sub>-C<sub>6</sub> alkyl group, such as benzyl, syclopentylmethyl, cyclohexylmethyl group and the like), a such as phenyl, naphthyl group and the like), an arylalkyl sycloalkenylalkyl group (e.g.,  $C_3-C_{\mathfrak{g}}$  cycloalkenyl -  $C_1-C_{\mathfrak{g}}$ cyclobutenyl, cyclopentenyl, cyclohexenyl group and the þe sycloalkenyl group having 3 to 8 carbon atoms such as can the like alkyl group, such as cyclobutenylmethyl, naphthylmethyl group and the like) and mentioned. 10

optionally having substituents" represented by R<sub>2</sub> and R<sub>3</sub>, a
5- to 12-membered monocyclic or fused heterocyclic group
containing 1 or 2 kinds of 1 to 4 hetero atoms selected
from nitrogen atom, sulfur atom and oxygen atom such as
pyridyl, pyrrolidinyl, piperazinyl, piperidinyl, 2oxazepinyl, furyl, decahydroisoguinolyl, quinolyl, indolyl,
isoguinolyl, thienyl, imidazolyl, morpholinyl etc., and the
like can be mentioned. As the substituent for the
"hydrocarbon group optionally having substituents" and

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"heterocyclic group optionally having substituents" for

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10 15 20 thiol group, a carboxyl group, a lower alkanoyl group (e.g., formyl;  $C_{1-6}$  alkyl-carbonyl group, such as acetyl, propionyl, alkoxycarbonyl group (e.g.,  $C_{1-6}$  alkoxy-carbonyl group, such aralkyloxy-carbonyl group, such as benzyloxycarbonyl group chlorine, bromine, fodine etc.), a lower alkyl group (e.g., ethyryi, propargyl group and the like), a cycloalkyl group (e.g., cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexy- group and the like), a lower alkoxy group (e.g., alkoxy group having as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl group phenyl, naphthyl group and the like), an aryloxy group 1 to 6 carbon atoms such as methoxy, ethoxy group and the and the like), an aryl group (e.g., Cein aryl group, such ethyl, propyl group and the like), a lower alkeryl group rinyl, allyl group and the like), a lower alkynyl group (e.g., alkynyi group having 2 to 6 carbon atoms such as butyryl group and the like), a lower alkanoyloxy group (e.g., formyloxy;  $C_{1-6}$  alkyl-carbonyloxy group, such as and the like), an aralkyloxycarbonyl group (e.g.,  $C_{7-1}$ alkyl group having 1 to 6 carbon atoms such as methyl, like), a nitro group, a cyano group, a hydroxy group, (e.g., alkenyl group having 2 to 6 carbon atoms such acetyloxy, propionyloxy group and the like), a lower and R3, for example, a halogen atom (e.g., fluorine, (e.g., C<sub>6-1</sub>, aryloxy group having, such as phenyloxy,

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limethylamino, ethylamino, diethylamino group etc., and the substituents (e.g., carbamoyl; carbamoyl group mono- or diposition of the substitutions are not particularly limited. substituted by alkyl group having 1 to 6 carbon atoms such like), an amino group optionally having substituents (e.g., (e.g., C<sub>6-14</sub> aryl-carbonyl group, such as benzoyl, naphthoyl as methylcarbamoyl, dimethylcarbamoyl group etc., and the amino; aminc group mono- or di-substituted by alkyl group ဂ ရ-<sub>14</sub> aryl-carbonyloxy group, such as benzoyloxy, naphthoyloxy group and the like), a carbamoyl group optionally having The number and the naphthyloxy group and the like), an arylcarbonyl group group and the like), an arylcarbonyloxy group (e.g., naving 1 to 6 carbon atoms such as methylamino, like) and the like can be mentioned.

mentioned E, R,  $R_1$  and G may have 1 to 5, preferably 1 to 3, substituents is not less than 2, each substituents are the the aforementioned substituent at substitutable positions optionally having substituents" represented by the above-The "hydrocarbon group" of the "hydrocarbon group of the hydrocarbon group, wherein, when the number of

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setrahydroquinoline, tetrahydroisoquinoline and the like

can be mentioned.

piperidine, homopiperidine, morpholine, piperazine,

As the ring formed by R, and R, together with the

pyrrolidine,

adjacent nitrogen atom, for example,

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same or different.

As the "heterocyclic group" of the "heterocyclic group heterocyclic group containing, as ring atoms, 1 to 4, more preferably 1 to 3, hetero atoms selected from oxygen arom, to 3) hetero atoms selected from oxygen atom, sulfur atom constituting atom (ring atom), 1 to 3 (preferably 1 or 2) kinds of at least 1 (preferably 1 to 4, more preferably 1 optionally having substituents" represented by the aboveand nitrogen atom and the like can be mentioned. As the preferable, particularly a 5- to 12-membered saturated oxygen-containing heterocyclic group and the like are sulfur atom and nitrogen atom etc., and the like are heterocyclic group and saturated or unsaturated nonmentioned above, as the "heterocyclic group" of the "heterocyclic group optionally having substituents" mentioned E, R and G, a 5- to 12-membered aromatic momatic heterocyclic group containing, as ringrepresented by G, a saturated oxygen-containing preferable.

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As the "aromatic heterocyclic group", an aromatic heterocyclic group and the like can be mentioned. monocyclic heterocyclic group, an aromatic fused

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As the "aromatic monocyclic heterocyclic group", for heterocyclic group such as furyl, thienyl, pyrrolyl, example, a 5- or 6-membered aromatic monocyclic

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)xazolyl, isooxazolyl, thiazolyl, isothiazolyl, imidazolyl,

chiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl etc., and the like can be mentioned. pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4oxaciazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-

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aronatic monocyclic heterocyclic group are condensed), such neterocyclic groups of the aforementioned 5- or 6-membered example, a 8- to 12-membered aromatic fused heterocyclic heterocyclic group is condensed with a benzene ring, or As, the "aromatic fused heterocyclic group", for or different two aforementioned 5- or 6-membered aromatic monocyclic group (preferably a heterocyclic group wherein the heterocyclic group wherein the same

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senzothiszolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 1H-indazolyl, penzimidazolyl, benzoxazolyl, 1,2-benzolsoxazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, as benzofuranyl, isobenzofuranyl, benzothienyl,

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ohenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, eteridinyl, carbazolyl,  $\alpha$ -carbolinyl,  $\beta$ -carbolinyl,

pyrazolo[1,5-a]pyridyl, imicazo[1,2-a]pyridyl, imidazo[1,5-

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alpyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrididinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl etc., and the like can be mentioned.

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(aliphatic heterocyclic group) such as oxylanyl, azetidinyl, examples thereof include 2-oxoazetidiny1, 2-oxopyrrolidinyl. oxotetrahydrofuryl, 2-oxotetrahydropyranyl, 2-oxothiolanyl, oxocanyl, thiocanyl, oxazocanyl, thiazocanyl and the like heterocyclic group such as 2-oxopyrrolidinyl and the like A 5-membered non-aromatic oxepanyl, thiepanyl, oxzzepanyl, thiazepanyl, azocanyl, (preferably saturated) non-aromatic heterocyclic group (preferably 5- or 6-membered) saturated or unsaturated neterocyclic group", for example, a 3- to 8-membered morpholinyl, thiomorpholinyl, piperazinyl, azepanyl, can be mentioned. These may be oxo-substituted and oxooxazepanyl, 2-oxothiepanyl, 2-oxothiazepanyl, 2thiolanyl, piperidinyl, tetrahydropyranyl, thianyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, As the "saturated or unsaturated non-aromatic 2-oxothianyl, 2-oxopiperazinyl, 2-cxooxepanyl, 2oxooxocanyl, 2-oxothiocanyl, 2-oxooxazocanyl, 2-2-oxopiperidinyl, 2-oxazepanyl, 2-oxazocanyl, oxothiazocanyl and the like. preferable. 1s

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As the substituent that the "heterocyclic group" of

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the "heterocyclic group optionally having substituents" represented by the above-mertioned E, R and G may have, for example, those similar to the "substituent" of the

5 represented by the aforementioned E, R, R, and G and the like are used.

'hydrocarbon group optionally having substituents"

The "heterocyclic group" of the "heterocyclic group optionally having substituents" represented by E, R and G may each have 1 to 5, preferably i to 3, substituents mentioned above at substitutable positions of the heterocyclic group, and when the number of substituents is two or more, the substituents are the same or different.

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The bond between R and W in the compound of the present invention is explained below. When R and W are bonded, the position of the bond between R and W is not particularly limited as long as R and W can be bonded. The bondable position of R is the position where the "hydrocarbon group" and "substituent" of the "hydrocarbon group optionally having substituents" defined above for R can be bonded, and the position where the "heterocyclic group" and "substituent" of the "heterocyclic group optionally having substituents" defined above for R can be optionally having substituents" defined above for R can be

As the bondable position of  $W_{\star}$  a bondable position of the "divalent chain hydrocarbon group" of the "divalent

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bonded.

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R and W can be bonded at the bondable position thereof and can form a ring together with the adjacent nitrogen atom. As such ring, for example, a saturated nitrogencontaining ring (e.g., azetidine, pyrrolidine, piperidine, homopiperidine etc.), an unsaturated nitrogen-containing ring (e.g., tetrahydropyridine etc.), a netero ring (e.g., piperazine, morpholine etc.) containing, besides the nitrogen atom to which R and W are adjacent, at least one hetero atom selected from the group consisting of nitrogen, oxygen and sulfur, a fused ring (e.g., indole, indoline, isoindole, isoindoline, tetrahydroquinoline, tetrahydroguinoline, tetrahydroguinoline, tetrahydroguinoline, tetrahydroguinoline etc.) and the like can be mentioned. Of these, a 4- to 7-membered ring is preferable.

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The ring formed by R and W, which are bonded at each bondable position thereof, together with the adjacent

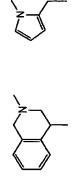
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nitrogen atom may have 1 to 4 substituents at substitutable positions thereof. When the number of substituents is 2 or more, the substituents are the same or different. As the substituent, the substituents of the "hydrocarbon group optionally having substituents" defined for R, and the substituents of the "divalent chain hydrocarbon group optionally having substituents" defined for W can be mentioned. Specifically, a halogen atom (e.g., fluorine, calorine, bromine, iodine etc.), a C<sub>i.e</sub> alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, tert-butyl, pentyl, 1-ethylpropyl, hexyl etc., and the like can be mentioned.

By the bond between R and W, for example,



These may have substituents as defined above, and it would be understood for those of ordinary skill in the and the like are formed, but the ring is not limited to art that they may also have an isomer. In the present invention, X represents a leaving group, dioxypyrrolidin-1-yl)oxy group and the like. Of these, a halogen atom such as fluorine, chlorine, bromine, iodine and the like is preferable, and chlorine is particularly such as a halogen atom, a benzotriazolyl group, a (2,5-

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preferable.

In the present invention, M represents a hydrogen atom, a metal cation or a quaternary ammonium ion.

In the present invention, the "metal cation" is exemplified by alkali metal ion (e.g., Na', K', Li', Cs' and the like), with preference given to Na.

tetrabutylammonium ion and the like, with preference given In the present invention, the "quaternary ammonium tetraethylammonium ion, tetrapropylammonium ion, ion" is exemplified by tetramethylammonium ion,

to tetrabutylammonium ion.

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formed between a basic group in a molecule and an inorganic molecule and an inorganic base or an organic base etc, and In the compound (II), a pharmacologically acceptable a pharmacologically acceptable acid addition salt can be basic salt can be formed between an acidic group in acid or an organic acid etc.

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include salt with alkali metal (e.g., sodium, potassium and Examples of the inorganic basic salt of compound (II) piperidine, 2-phenylethylamine, benzylamine, ethanolamine, diethanolamine, pyridine, collidine etc., and the like. the like), alkaline earth metal (e.g., calcium and the like), ammonia etc., and the like, and examples of the dimethylamine, triethylamine, piperazine, pyrrolidine, organic basic salt of compound (II) include salt with

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methanesulfonate, p-toluenesulfonate and the like) and the fumarate, propionate, citrate, tartrate, lactate, oxalate, include inorganic acid salt (e.g., hydrochloride, sulfate, Examples of the acid addition salt of compound (II) hydrobromide, phosphate and the like), organic acid salt (e.g., acetate, trifluoroacetate, succinate, maleate,

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The compound (II) of the present invention encompasses hydrates. Examples of the "hydrate" include 0.5 hydrate 5.0 hydrate. Of these, 0.5 hydrate, 1.0 hydrate, 1.5 nydrate and 2.0 hydrate are preferable.

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racemates and optically active compounds. As the optically active compound, such compound wherein one enantiomer is in enantiomer excess (e.e.) of not less than 90% is preforable, The compound (II) of the present invention encompasses more preferably in enantiomer excess of not less than 99%

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As an optically active form, an (R)-form represented by the formula:

As the preferable compounds encompassed in compound (II), wherein each symbol is as defined above, is preferable. for example, the following specific compounds can be mentioned. 2-[methy][[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

That is,

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2-[methy][[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-

yl]carbonyl]amino]ethyl acetate,

pyridyl]methyl]sulfinyl]-1H-benzimidazol-1yl]carbonyl]amino]ethyl trimethylacetate,

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2-[metnyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy]-2oyridyl]methyl]sulfinyl]-1H-benzimidazol-12-[methy][[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-15

/l]carbonyl]amino]ethyl cyclohexanecarboxylate,

yl]carbonyl]amino]ethyl benzoate,

2-[methy1[[2-[[[3-methy1-4-(2,2,2-trifluoroethoxy)-2pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

2-[methy1[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2oyridyl]methyl]sulfinyl]-1H-benzimidazol-1yl]carbonyl]amino]ethyl 4-methoxybenzoate, yl]carbonyl]amino]ethyl benzoate, 20

2-[methy][[(R)-2-[[[3-methy]-4-(2,2,2-trifluoroethoxy)-2pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

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yl]carbonyl]amino]ethyl 3-chlorobenzoate,

2-[methy1[[(R)-2-[[[3-methy1-4-(2,2,2-trifiuoroethoxy)-2-

pyridyl]methyl]sulfinyl]-lF-benzimidazol-1-

yl]carbonyl]amino]ethyl 3,4-difluorobenzoate,

5 2-[methy1[[(R)-2-[[[3-methy1-4-(2,2,2-trifluoroethoxy)-2-

pyridyl]methyi]sulfinyl]-1H-benzimidazol-1-

yl]carbonyl]amino]ethyl 4-trifluoromethoxybenzoate,

2-[methy1[[(R)-2-[[[3-methy1-4-(2,2,2-trifluoroethoxy)-2-

pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

10 yl]carbonyl]amino]ethyl 4-fluorobenzoate,

2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-

pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

yl]carbonyl]amino]ethyl 3,4,5-trimethoxybenzoate,

2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2,trifluoroethoxy]-2-

15 pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

yl]carbonyl]amino]ethyl 2-pyridinecarboxylate,

2-[methy1[[(R)-2-[[[3-methy1-4-(2,2,2-trifluoroethoxy)-2-

pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

yl]carbonyl]amino]ethyl methoxyacetate,

20 ethyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-1H-

benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,

isopropyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

trifluoroethoxy)-2-pyridyl]methyl]sulfinyl}-1H-

25 benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,

isopropyl 2-[methyl[[2-[[[3-methyl-4-(2,2,2-

trifluoroethoxy > 2-pyridyl]methyl]sulfinyl]-lH-

benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,

benzyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

5 trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lH-

benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,

2-[methy][[(R)-2-[[[3-methy]-4-(2,2,2-trifluoroethoxy)-2-

pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

yl]carbonyl]amino]ethyl tetrahydropyran-4-yl carbonate,

10 2-methoxyethyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-,

trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,

2-[ethyl[[(R)-2-[[[3-methy-4-(2,2,2-trifluoroethoxy)-2-

pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

15 yl]carbonyl]amino]ethyl acetate,

2-[isopropy1[[(R)-2-[[[3-methy1-4-(2,2,2-trifluoroethoxy)-

2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

yl]carbonyl]amino]ethyl acetate,

ethy: 2-[isopropy][[(R)-2-[[[3-methy1-4-(2,2,2-

20 trifluoroethoxy)-2-pyridy\_]methyl]sulfinyl]-1H-

benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,

2-[cyclohexy1[[(R)-2-[[[3-methy1-4-(2,2,2.trifluoroethoxy)-

2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

yl]carbonyl]aminojethyl acetate,

25 2-[cyclohexyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-

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2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1yl]carbonyl]amino]ethyl ethyl carbonate, 2-[[[(R)-2-4[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

yl]carbonyl] (phenyl) amino]ethyl acetate, 'n

2-[[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy]-2-

pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

yl]carbonyl](phenyl)amino]ethyl acetate,

tert-butyl [2-[methyl[[(R)-2-[[[3-methy]-4-(2,2,2-

- trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-1H-10

benzimidazol-1-yl]carbonyl]amino]-3-pyridyl]methyl

carbonate,

2-[methy1[[(R)-2-[[[3-methy1-4-(2,2,2-trifluoroethoxy]-2-

pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

yl]carbonyl]amino]benzyl acetate, 15 2-[[2-(acetyloxy)ethyl][[(R)-2-[[[3-methyl-4-(2,2,2-

trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

benzimidazol-1-yl]carbonyl]amino]ethyl acetate,

[(2S)-1-[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-

pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]-2-20

ethyl [methyl:[[R]-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyrrolidinyl]methyl acetate,

2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

/l]carbonyl]amino]acetate,

2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-25

3-[methy1[[(R)-2-[[[3-methy1-4-(2,2,2-trifluoroethoxy)-2pyridyl)methyl]sulfinyl]-1H-benzoimidazol-1pyridyl]methyl]sulfinyl]-1H-benzimidazol-1yl]carbonyl](methyl)amino]ethyl benzoate,

yl]carbonyl]amino]propyl benzoate, Ŋ

?-[methy][[2-[[[3-methy]-4-(2,2,2-trifluoroethoxy]~2-

oyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

yl]carbonyljamino]ethyl tetrahydropyran-4-yl carbonate,

sthyl 2-[methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy]-2-

yl]carbonyl]amino]ethyl carbonate,

pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

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ethyl 2-[methyl[[(S)-2-[[[[3-methyl-4-(2,2,2-

trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

>enzimidazol-1-yl]carbonyl]amino]ethyl carbonate,

ethyl 2-[[[5-methoxy-2-][(4-methoxy-3,5-dimethyl-2-15

pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-

2-[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-

yl]carbonyl](methyl)amino]ethyl carbonate,

oyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-

y\_]carbonyl](methyl)amino]ethyl acetate, 20

2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-

pyridyl)methyl]sulfinyl]-3K-imidazo[4,5-b]pyridin-3-

yl]carbonyl](phenyl)amino]ethyl acetate,

4-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-

pyridyl]methyl]sulfinyl]-lH-benzimidazol-1-25

89

yl]carbonyl]amino]butyl acetate,
ethyl 4-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl:-lH-

benzimidazol-1-yl]carbonyl]amino]butyl carbonate,

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ethyl 3-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazol-1-yl]carbonyl]amino]propyl carbonate,
3-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

10 yl]carbonyl]amino]propyl acetate,
3-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lH-benzimidazol-lyl]carbonyl]amino]propane-1,2-diyl diacetate,
diethyl 3-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

15 trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H benzimidazol-1-yl]carbonyl]amino]propane-1,2-diyl
 biscarbonate,

2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-

pyr\_dyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3yl]carbonyl](methyl)amino]ethyl 3-chloropenzoate,
2-[methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-bonzimidazol-1yl]carbonyl]amino]ethyl acetate,

2-ethoxyethyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,225 trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lH-

benzimidazol-1-yl]carbonyl]amino]ethyl carbonate,

3-methoxypropyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-lH-

benzimidazol-1-yl]carbonyl!amino]ethyl carbonate,

5 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2pyridyl]methyl]sulfinyl]-lH-benzimidazol-1-

yl)carbonyl]aminolethyl N,N-dimethylglycinate,
S-[2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-

2-pyridyl]metnyl]sulfinyl]-1H-benzimidazol-1-

10 yl]carbonyl]amino]ethyl] thioacetate,

ethyl 2-[2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lHbenzimidazol-1-yl]carbonyl]aminolethoxylethyl carbonate,

ethyl 2-[methyl[[2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

15 trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazol-1-

yl]carbonyl]amino]ethoxy]carbonyl]amino]ethyl carbonate, ethyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-lH-benzimidazol-1-

yl]carbonyl](methyl)amino]ethyl carbonate,
2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl)methyl]sulfinyl]-lH-benzimidazol-1yl]carbonyl](phenyl)amino]ethyl acetate,

ethyl 2- [[(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-

pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-

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ethyl 2-[[[2-[[[4-(3-methoxypropoxy)-3-methyl-2pyridyl]methyl]sulfinyl]-1H-benzimidazol-1yl]carbonyl](methyl)amino]ethyl carbonate, yl]carbonyl](methyl)amino]ethyl carbonate,

2-[[[5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2pyridyl)methyl]sulfinyl]-1H-Senzimidazol-1oyridyl]methyi]sulfinyl]-1H-benzimidazol-1-2-[[[2-[[[4-(3-methoxypropoxy)-3-methyl-2yl]carbonyl](phenyl)amino]ethyl acetate,

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- 2-[methy1[[(R)-2-[[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2yl]carbonyl]amino]ethyl 1-methylpiperidine-4-carboxylate, 2-['4-(aminocarbonyl)phenyl][[(R)-2-[[[3-methyl-4-(2,2,2yl]carbonyl](methyl)amino]ethyl ethyl carbonate, pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-10
  - 2-[methy1[[(R)-2-[[[3-methy1-4-(2,2,2-trif]uoroethoxy)-2yl]carbonyl]amino]ethyl 1-methyl-4-piperidinyl carbonate, benzimidazol-1-yl]carbonyl]amino]ethyl acetate, trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hpyridyl]methyl]sulfinyl}-1H-benzimidazol-1-13
- (-)-ethyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-2-[[4-(aminocarbony])phenyl][[2-[[[3-methyl-4-(2,2,2pyridy1)methy1]sulfiny1]-3H-imidazo[4,5-b]pyridin-3trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-1Hbenzimidazol-1-yl]carbonyl]amino]ethyl acetate, 20

yl]carbonyl] (methyl) amino]ethyl carbonate and

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yl]carbonyl](methyl)amino]ethyl carbonate, a salt thereof (+)-ethyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3and the like can be mentioned.

- 2-[methy1[[(R)-2-[[[3-methy]-4-(2,2,2-trifluoroethoxy)-2-Of these, the following compounds and salts thereof are pyridy[]methy]]sulfinyl]-1H-benzimidazol-1yl]carbonyl]amino]ethyl acetate, preferable.
- 2-[methy1[[(R)-2-[[[3-methy1-4-(2,2,2-trifluoroethoxy)-2benzimidazol-1-yl]carbonyl]amino]ethyl carbonate, :rifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-1Hethyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-10
- ethy\_ 2-[methy][[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy]-2yl]carbonyl]amino]ethyl tetrahydropyran-4-yl carbonate, yl]carbonyl]amino]ethyl tetrahydropyran-4-yl carbonate, 2-[methy1[[2-[[[3-methy1-4-(2,2,2-trifluoroethoxy)-2oyridyl]methyl]sulfinyl]-1H-benzimidazól-1-15
  - oyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3sthyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl]methyl]sulfinyl]-1H-benzimidazol-1yl]carbonyl](methyl)amino]ethyl carbonate, yl]carbonyl]amino]ethyl carbonate, 20
- 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-25

oyridyl)methyljsulfinyl]-3H-imidazo[4,5-b]pyridin-3-/l]carbonyl](methyl)amino]ethyl acetate, 2-[methy1[[2-[[[3-methy1-4-(2,2,2-trifluoroethoxy]-2pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

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ethy\_ 2-[[[(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2ethyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl)methyl]sulfinyl]-1H-benzimidazol-lyl]carbonyl](methyl)amino]etnyl carbonate, yl]carbonyl]amino]ethyl acetate,

ethyl 2-[[[2-[[[4-(3-methoxypropoxy)-3-methyl-2yl]carbonyl](methyl)amino]ethyl carbonate, and pyridyl)methyl]sulfinyl]-îH-benzimidazol-1pyridyl]methyl]sulfinyl]-1H-benzimidazol-1yl]carbonyl](methyl)amino]ethyl carbonate,

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yl]carbonyl](methyl)amino]ethyi ethyl carbonate. 2-[[[5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2pyridyl)methyl]sulfinyl]-lH-benzimidazol-1-

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The compound (II) can be produced by the following

m. method A or 20

(Method A)

The compound (II) or a salt thereof can be obtained by compound (V) or a salt thereof in the presence or absence condensation of compound (IV) or a salt thereof with

of a base. The salt of compound (IV) and the salt of

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such as inorganic acid salt (e.g., hydrochloride, sulfate, salts of compound (II). For example, acid addition salts compound (V) here are exemplified by the above-mentioned hydrobromide, phosphate and the like), organic acid salt

methanesulfonate, p-toluenesulfonate and the like), and the 'umarate, propionate, citrate, tartrate, lactate, oxalate, (e.g., acetate, trifluoroacetate, succinate, maleate, be mentioned.

Method A is generally conducted in a solvent, and a solvent etrachloride, trichlene, 1,2-dichloroethane and the like), that does not inhibit the reaction of Method A is selected (e.g., dioxane, tetrahydrofuran, diethyl ether, tert-butyl wherein each symbol is as defined above. The reaction of methyl ether, diisopropyl ether, ethylene glycol dimethyl is appropriate. Examples of such solvent include ethers hydrocarbons (e.g., dichloromethane, chloroform, carbon hydrocarbons (e.g., n-hexane, benzene, toluene and the ether and the like), esters (e.g., ethyl formate, scetate, butyl acetate and the like), halogenated ព 15

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like), amides (e.g., formamide, N,N-dimethylformamide, N,N-dimethylacetamide and the like), ketones (e.g., acetone, methyl isobutyl ketone and the like), nitriles (e.g., acetonitrile, propionitrile and the like) and the like, as well as dimethyl sulfoxide, sulfolane, hexamethylphosphoramide, water and the like, which may be used alone or as a mixed solvent. The amount of the solvent to be used is not particularly limited as long as the reaction mixture can be stirred, which is generally 2-to 100-fold amount by weight, preferably 5- to 50-fold amount by weight, relative to 1 mole of compound (IV) or a salt thereof.

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The amount of compound (IV) or a salt thereof to be used is generally 1 - 10 mole, preferably 1 - 3 mole, relative to 1 mole of compound (IV) or a salt thereof.

The reaction of Method A is carried out within a temperature range of from about 0°C to 100°C, preferably 20°C to 80°C.

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The reaction time of Method A varies depending on the kind of compounds (IV), (V) or a salt thereof and solvent, reaction temperature and the like, but it is generally 1 min. - 96 hrs., preferably 1 min. - 72 hrs., more preferably 15 min. - 24 hrs.

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The base in Method A is, for example, an inorganic base (e.g., sodium carbonate, potassium carbonate, calcium

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carbonate, sodium hydrogen carbonate etc.), a tertiary amine (e.g., triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, pyridine, lutidine, \( \gamma \cdot \)-dimcthylaniline, \( N \cdot \)-methylpiperidine, \( N \cdot \)

dimethylaminopyridine and the like); alkylene oxides (e.g., propylene oxide, epichlorohydrin etc.) and the like. The amount of the base to be used is generally 1 mole - 10 mole, preferably 1 mole - 3 mole, relative to 1 mole of compound

The compound (IV) or a salt thereof can be produced according to the method described in JP-A-61-50978, USP 4,628,098 and the like or a method similar thereto.

or a salt thereof.

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The compound (V) or a salt thereof can be produced according to a method known per se or a method analogous thereto. For example, when X is a chlorine atom, compound (V) can be obtained by reacting a compound represented by the formula (VII):

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wherein each symbol is as defined above, or a salt thereof with phosgene, trichloromethyl chloroformate, bis(trichloromethyl)carbonate, thiophosgene and the like in the presence of an acid scavenger in a solvent (e.g., tetrahydrofuran, acetonitrile, dichloromethane etc.).

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Alternatively, compound (V) can be also obtained by reating ethylcarbamate, which is obtained by reacting compound (VII) or a salt thereof with ethyl chloroformate,

with phosphorus oxychloride according to the method

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described in Synthetic Communications, vol. 17, p. 1887 (1967) or a method analogous thereto. As the salt of compound (VII), for example, acid addition salts such as inorganic acid salts (e.g., hydrochloride, sulfate, hydrobromide, phosphate etc.), organic acid salts (e.g., acetate, trifluoroacetate, succinate, maleate, fumarate, propionate, citrate, tartrate, lactate, oxalate, methanesulfonate, p-toluenesulfonate etc.), and the like can be mentioned.

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As the acid scavenger used here, for example, inorganic bases (e.g., sodium carbonate, potassium carbonate, calcium carbonate, sodium hydrogen carbonate etc.), tertiary amine (e.g., triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, pyridine, lutidine, y-collidine, N.N-dimethylamiline, N-methylpiperidine, N-methylpiperidine, A-dimethylaminopyridine etc.) and the like can be menticned. The compound (VII) and a salt thereof can be produced according to a method known per se or a method analogous thereto. For example, when D, is other than a bond,

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represented by the formula (VIII):

(VIII)

wherein R, is a hydrogen atom or nitrogen-protecting group, and other symbols are as defined above, or a salt thereof with carboxylic acid or thionic acid represented by the

Х ||-|G-D<sub>2</sub>-С-ОН

formula (IX):

(XI)

wherein each symbol is as defined above, or a reactive derivative thereof (e.g., anhydride, halide etc.), or a salt thereof in a suitable solvent (e.g., ethyl acetate, tetrahydrofuran, dichloromethane, N.N-dimethylformamide etc., followed by deprotection as necessary. As the salt of compound (VIII), for example, acid addition salts such as inorganic acid salts (e.g., hydrochloride, sulfate,

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hydrooromide, phosphate etc.), organic acid salts (e.g., acetate, trifluoroacetate, succinate, maleate, fumarate, propionate, citrate, tartrate, lactate, oxalate, methanesulfonate, proluenesulfonate etc.) etc., and the like can be mentioned.

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Alternatively, when  $D_1$  is a bond, compound (VII) can be obtained by condensing carboxylic acid or thionic acid represented by the formula (X):

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compound (VII) can be obtained by condensing a compound

wherein each symbol is as defined above, or a reactive derivative thereof (e.g., anhydride, halide etc.), or a salt thereof with a compound represented by G-D<sub>2</sub>-H in a suitable solvent (e.g., ethyl acetate, tetrahydrofuran, dichloromethane, N.N-dimethylformamide etc.), followed by deprotection, as necessary. As the salt of compound (X), for example, acid addition salts such as inorganic acid salts (e.g., hydrochloride, sulfate, hydrobromide,

phosphate etc.), organic acid salts (e.g., acetate, trifluoroacetate, succinate, maleate, fumarate, propionate, citrate, tartrate, lactate, oxalate, methanesulfonate, p-toluenesulfonate etc.) and the like, salts with alkali metal (e.g., sodium, potassium etc.), alkaline earth metal (e.g., calcium etc.), ammonia etc., and the like, and for example, organic base such as dimethylamine, triethylamine, piperazine, pyrrolidine, piperidine, 2-phenylethylamine, benzylamine, ethanolamine, diethanolamine, pyridine, collidine etc., and the like can be mentioned.

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As the protecting group represented by  $R_4$  in the formula (VIII) and the formula (X), for example, a formyl group, a  $C_{1-6}$  alkyl-carbonyl group (e.g., acetyl, ethylcarbonyl etc.), a benzyl group, a tertbutyloxycarbonyl group, a benzyloxycarbonyl group, an

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allyloxycarbonyl group, a C<sub>7-10</sub> aralkyl-carbonyl group (e.g., benzylcarbonyl etc.), a trityl group and the like are used. These groups may be substituted by 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine etc.), a nitro group and the like.

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As a method for removing such protecting groups, a method known per se or a method analogous thereto is used, which is, for example, a method using an acid, a base, reduction, UV light, palladium acetate etc., and the like

10 are used.

(Method B)

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The compound (II) and a salt thereof can be obtained by subjecting compound (VI) or a salt thereof to oxidization reaction.

wherein each symbol is as defined above.

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The reaction in Method B can be carried out using an oxidant such as nitric acid, hydrogen peroxide, peroxyacid, peroxyacid ester, ozone, dinitrogen tetraoxide,

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generally 0.5 mole - 2 mole, preferably 0.8 mole - 1.2 mole, chlorine, sulfuryl chloride, magnesium monoperoxyphthalate ert-butyl hypochlorite, diazabicyclo[2.2.2]octane-bromine complex, sodium metaperiodate, selenium dioxide, manganese presence of a catalyst such as vanadium acetate, vanadium oxide acetylacetonate, titanium tetraisopropoxide and the oxidization may be carried out using the above-mentioned oxidant such as hydrogen peroxide and peroxyacids in the iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, dioxide, chromic acid, cerium ammonium nitrate, bromine, and the like. The amount of the oxidant to be used is per 1 mole of compound (VI) or a salt thereof. like.

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The reaction of Method B is generally carried out in a ketones (e.g., acetone, methyl ethyl ketone etc.), nitriles The "inert solvent" is used in dioxane, tetrahydrofuran etc.), sulfoxides (e.g., dimethyl diethyl ether, tert-butyl methyl ether, diisopropyl ether, hexamethylphosphoramide etc.), which may be used alone or solvent inert to the above-mentioned oxidation reaction. Examples of the "inert solvent" include water, alcohols (e.g., methanol, ethanol, 1-propanol, 2-propanol etc.), (e.g., acetonitrile, propionitrile etc.), amides (e.g., formamide, N,N-dimethylformamide etc.), ethers (e.g., sulfoxide etc.) and polar solvents (e.g., sulfolane, as a mixed solvent thereof.

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generally 1- to 100-fold amount by weight of compound (VI) or a salt thereof.

The reaction temperature is generally from  $-80^{\circ}\text{C}$  to 80°C, preferably from 0°C to 30°C.

The reaction time is generally 1 min. - 6 hrs., preferably 15 mins. - 1 hr.

Method B, can be obtained by a reaction similar to that in The compound (VI), which is a starting material in 4ethod A, by the use of, for example, a compound

represented by the following formula (XI):  $\Xi$ 

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wherein each symbol is as defined above, instead of compound (IV). The compound (XI) can be synthesized according to the nalogous thereto: JP-A-61-50978, JP-A-54-141783, JP-A-61methods described in the following references or a method 22079, JP-A-1-6270, JP-A-63-146882.

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succinate, maleate, fumarate, propionate, citrate, tartrate, The salt of compound (VI) is exemplified by the abovetrifluoroacetate, lydrochloride, sulfate, hydrobromide, phosphate and the mentioned salts of the compound (II), which are acid addition salts such as inorganic acid salt (e.g., like), organic acid salt (e.g., acetate,

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lactate, oxalate, methanesulfonate, p-toluenesulfonate and the like) and the like.

The compound (II) or a salt thereof obtained by the above-mentioned methods A or B can be isolated and purified from the reaction mixture by a separation means known per se (e.g., concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like). Since compound (II) and a salt thereof obtained by the above-mentioned methods A or B encompass any isomers thereof, optically pure compound (II) and a salt thereof can be obtained by, for example, subjecting compound (II) or a salt thereof. cxidation of compound (VI) or a salt thereof.

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The method of optical resolution includes methods known per se, such as a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth. Asymmetric oxidation includes methods known per se, such as the method described in WO96/02535 and the like.

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The "fractional recrystallization method" includes a method in which a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-l-phenethylamine, (-)-l-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.], which salt is separated by

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fractional recrystallization etc., and, if desired, subjected to a neutralization process to give a free optical isomer.

The "chiral column method" includes a method in which a racemate or a salt thereof is applied to a column for optical isomer separation (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a racemate to a chiral column such as ENANTIO-OVM (produced by Tosoh Corporation), the DAICEL

CHIRAL series (produced by Daicel Corporation) and the like, and developing the racemate in water, a buffer (e.g., phosphate buffer), an organic solvent (e.g., hexane, ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, triethylamine, etc.),

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or a solvent mixture thereof. In the case of gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (produced by GL Science) and the like is used to separate optical isomers.

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"diastereomer method" includes a method in which a give a diastereomeric mixture, which is then subjected to recrystallization, chromatography, etc.) to obtain either fractional reacted a chemical are (e.g., racemate and an optically active reagent t t subjected means is separation diastereomer, which ordinary

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(e.g., acid hydrolysis, base hydrolysis, hydrogenolysis,

Said (trifluoromethyl)phenylacetic acid], (-)-menthoxyacetic acid and the like, optically active alkoxymethyl halides optically active reagent" includes, for example, optically (iR-endo)-2-(chloromethoxy)-1,3,3moiety, [a-methoxy-aobtained. stc.) to cut off the optically active reagent trimethylbicyclo[2.2.1]heptane etc., and the like. MTPA whereby the desired optical isomer is as such acids organic active

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Further, a benzimidazole compound represented by the following general formula (III) or a salt thereof is also mentioned as the specific example of the above-mentioned prodrug.

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In the above-mentioned formula (III), D indicates an oxygen atom or a bond, and Q indicates a hydrocarbon group optionally having a substituent group.

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The "hydrocarbon group" of the "hydrocarbon group optionally having a substituent group" represented by Q includes an aliphatic or aromatic hydrocarbon group, and an

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means a cyclic alkynyl group, a C, cycloalkyl group and a C, aryl group a C3-e cycloalkyl group hydrocarbon group having I to 14 carbon atoms, and for alkyl group and a  $C_{3-\epsilon}$  cycloalkyl group are more preferred. group is preferably and a  $C_{\varepsilon^{-1}\ell}$  aryl group are preferred, and above all example, a  $C_{1-6}$  alkyl group, a  $C_{2-6}$  alkenyl group, or hydrocarbon group mentioned here unsaturated, lincar, branched The hydrocarbon are exemplified. A C1-6 alkyl group, hydrocarbon group. or aliphatic saturated

branched alkyl group, preferably an alkyl group having 1 to like are exemplified. An alkyl group having 1 to 4 carbon a linear or 3,3-dimethylbutyl, 3,3-dimethylpropyl, 2-ethylburyl and the isopropyl and tert-butyl are preferred, and tert-butyl is atoms is preferred. Among these, in Q, methyl, ethyl, carbon atoms (" $C_{1-6}$  alkyl group") and for example, methyl, cert-butyl, n-pentyl, isopentyl, neopentyl, 1-methylpropyl, n-hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, i,s The above-mentioned "alkyl group" preferred particularly. 20 2 15

The above-mentioned "C<sub>2-6</sub> alkenyl group" is a linear or branched alkenyl group having 2 to 6 carbon atoms. Example thereof includes vinyl, n-propenyl, isopropenyl, n-butenyl, isobutenyl, n-pentenyl, lesc-butenyl, l-methylpropenyl, n-hexenyl, n-hexenyl,

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isohexenyl, 1,1-dimethylbutenyl, 2,2-dimethylbutenyl, 3,3-dimethylbutenyl, 3,3-dimethylpropenyl, 2-ethylbutenyl and the like. An alkenyl group having 2 to 4 carbon atoms is preferred and vinyl, n-propenyl and isopropenyl are preferred particularly.

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butynyl, tert-butynyl, n-pentynyl, isopentynyl, neopentynyl, 1,1alkynyl group having 2 to 3 carbon atoms is preferred and preferred A. The above-mentioned " $C_{2-6}$  alkinyl group" is a linear or branched alkinyl group having 2 to 6 carbon atoms. Example (i-propynyl), Secdimethylbutynyl, 2,2-dimethylbutynyl, 3,3-dimethylbutynyl, like. isopropynyl (2-propynyl), n-butynyl, isobutynyl, isohexynyl, the are and n-propyny 2-propynyl 3,3-dimethylpropynyl, 2-ethylbutynyl n-hexynyl, ethynyl, and ethynyl, 1-propynyl includes l-methylpropynyl, particularly. thereof

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Example cycloalkyl group having 5 to 7 carbon atoms is preferred and among them, cyclopentyl, cyclohexyl and cycloheptyl are cyclopentyl, 13 the like. group" atoms. preferred. Cyclohexyl is preferred particularly. thereof includes cyclopropyl, cyclobutyl, cycloalkyl cyclohexyl, cycloheptyl, cyclooctyl and 8 carbon ູ່ເສື້ອ ţ ო above-mentioned cycloalkyl group having

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preferably 1 to

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The above-mentioned "aryl group" is a monocyclic or condensed polycyclic aromatic hydrocarbon group, and

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preferably an aromatic hydrocarbon group having 6 to 14 carbon atoms ("C<sub>6-1</sub>, aryl group"). Example thereof includes phenyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl. An aromatic hydrocarbon group having 6 to 10 carbon atoms is preferred, and phenyl is particularly preferred in Q.

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ئ ئ the ä þ amino group substituted, and examples of the substituent group include, ior example, a C<sub>6-14</sub> aryl group, a hydroxyl group, a halogen, may be substituted with a  $C_{1-6}$  alkyl group, and dronb, group, a The above-mentioned "hydrocarbon group" alkoxy-carbonyl a:  $C_{1-6}$  alkoxy C<sub>1-6</sub> alkyl group, optionally halogenated ្ដ пđ halogenated aralkyloxy group, optionally which may like.

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Examples of the substituent group in the "alkyl group optionally having a substituent group" include, for example, an aryl group, a hydroxyl group, a halogen, an alkoxy group which may be substituted with 1 to 5 halogens, a  $C_{1-12}$  aralxyloxy group, a  $C_{1-2}$  alkoxy-carbonyl group, and the like. The number of said substituent group is 1 to 5 and

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Examples of the substituent group in the "aryl group optionally having a substituent group" include a halogen, an alkyl group which may be substituted with 1 to 5 halogens, an aryl group, a hydroxyl group, an alkoxy group which may be substituted with 1 to 5 halogens, a C,22

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aralkyloxy group, a  $C_{1-s}$  alkoxy-carbonyl group, and the like. The number of said substituent group is 1 to 5 and preferably 1 to 3.

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C<sub>7-12</sub> said (vii) and " $C_{2-G}$  alkinyl group" may be substituted, and an þ substituted with a  $C_{1-6}$  alkyl group, and the like, and among "C2-6 alkenyl examples of the substituent group include (i) a  $C_{6-14}$  aryl (TA) an acylamino group, (viii) an amino group which may ø οţ aralkyloxy group, (vi) a C1-5 alkoxy-carbonyl group, (iii) a halogen, <u>A</u> preferred. The number substituent group is 1 to 5 and preferably 1 to 3. above-mentioned " $C_{1-6}$  alkyl group", group, C<sub>1-6</sub> alkoxy a hydroxy' group, are halogenated (vii) t t (ii) (i, optionally drozb,

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the and and "C<sub>6-14</sub> to (vii) are preferred particularly. The number of said substituent group is 1 to optionally a C<sub>1-5</sub> alkoxy-carbonyl group, (vii) a C<sub>1-6</sub> alkyl group amino nalogenated  $C_{1-6}$  alkoxy group, (v) a  $C_{1-12}$  aralkyloxy group, (11)group which may be substituted with a  $C_{1-6}$  alkyl group, οţ (viii) an group, examp\_es The above-mentioned " $C_{3-\theta}$  cycloalkyl group" an C<sub>6-14</sub> aryl halogen, (iv) be substituted with halogen, be substituted, and <u>:</u> (i) a the like, and among these, hydroxyl group, (iii) a include and preferably 1 to 3. substituent group may group" which may aryl (vi)

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group, a C2-6 alkenyl group and a C2-6 alkinyl group, which (iii) a halogen, (iv) an optionally halogenated C1-, alkoxy C<sub>1-6</sub> alkoxydroz6 (ii) a hydroxyl from group, (v) a C,-12 aralkyloxy group, (vi) a carbonyl group and (vii) an acylamino group, selected group, group a C<sub>6-14</sub> aryl substituent (Ţ) consisting of ส ស

or a C<sub>3-6</sub> cycloalkyl group or a C<sub>6-14</sub> aryl group, which may have a substituent selected from the group consisting of (i) a C<sub>6-14</sub> aryl group, (ii) a hydroxyl group, (iii) a halogen, (iv) an optionally halogenated C<sub>1-6</sub> alkoxy group, (v) a C<sub>7-12</sub> aralkyloxy group, (vi) a C<sub>1-5</sub> alkoxy-carbonyl group, and (vii) an optionally halogenated C<sub>1-6</sub> alkyl group.

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(v) a  $C_{1-6}$  alkoxy group which may be substituted with 1 to 5 þe (ii) a 5 substituent groups selected from the group substituted with 1 to 5 halogens, (v) a  $C_{r-12}$  aralkyloxy а С<sub>6-1</sub>4 groups is more preferably (1) a  $C_{1-6}$  alkyl group which may consisting of (i) a C<sub>6-14</sub> aryl group, (ii) a hydroxyl group, dnozb ç may (i) a halogen, or (2) nalogens, (iii) a C<sub>6-14</sub> aryl group, (iv) a hydroxyl and (vii) group which .5 substituent with group which may be substituted group and (vi) a C<sub>1-6</sub> alkoxy-carbonyl group, drozb C<sub>1-6</sub> alkoxy selected from the group consisting of ဌ a C,\_1, aralkyloxy aryl group which may have l (iv) a a halogen, (vi) have 1 to C1-6 alkyl halogens, (iii)

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25 alkoxy-carbonyl group.

the formula (III), Q is preferably a C1-6 alkyl

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and group (v) a C<sub>7-12</sub> cycloalkyl group or a C6-14 aryl group, which may have a Q is further more preferably a  $C_{1-6}$  alkyl group which (iii) a halogen,  $(\dot{\cdot} v)$  an optionally halogenated  $C_{1-\varepsilon}$  alkoxy a C<sub>1-5</sub> alkoxysubstituent group selected from the group consisting of (i) a C<sub>6-14</sub> aryl group, (ii) a hydroxyl group, (iii) a halogen, (i) a C<sub>6-1</sub>, aryl group, (ii) a hydroxyl group, carbonyl group and (vii) an acylamino group; or a group the (iv) an optionally halogenated  $C_{1-6}$  alkoxy group, selected from (vi) a C<sub>1-5</sub> alkoxy-carbonyl (vii) an optionally halogenated C1-6 alkyl group. (v) a C,-12 aralkyloxy group, (vi) a substituent group aralkyloxy group, consisting of have group,

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Among these, Q is preferably a  $C_{1-6}$  alkyl group which may be substituted with a  $C_{6-14}$  aryl group or a  $C_{6-14}$  aryl group, and Q is preferably phenyl group, methyl or textbutyl group in particular.

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In compound (III), an acidic group in the molecule can form a pharmacologically acceptable base salt with an inorganic salt or an organic salt or the like, and a basic group in the molecule can form a pharmacologically acceptable acid additive salt with an inorganic salt or an organic salt or the like.

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One preferable form of compound (III) of the present invention includes a compcund wherein D is a bond and Q is an alkyl group optionally having a substituent group or an

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aryl group optionally having a substituent group.

ohenylethylamine, benzylamine, ethanolamine, dietharolamine, example, sodium, potassium and the like), an alkali earth and Examples of the organic base salt of compound 2 metal (for example, calcium and the like); ammonia and the salts with dimethylamine, Examples of the inorganic base salt of compound (III) piperidine, metal an alkali pyrrolidine, example, salts with pyridine, collidine and the like. example, piperazine, include, for triethylamine, for (III)

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sulfate, hydrobromide, phosphate and the like), organic acid additive salt of compound (III) includes, for ď example, inorganic acid salts (for example, hydrochioride, example, acetate, trifluoroacetate, citrate, methanesulfoante, propionate, toluenesulfoante, and the like), etc. fumarate, oxalate, maleate, lactate, acid salts (for :artarate, succinate,

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The compound (III) of the present invention includes a hydrate. Said "hydrate" includes a 0.5 hydrate to 5.0 hydrates. Among these, 0.5 hydrate, 1.0 hydrate, 2.5 hydrates and 2.0 hydrates are preferred.

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The compound (III) of the present invention includes a racemic compound and an optically active compound.

As the optically active compound, such compound wherein one enantiomer is in enantiomer excess (e.e.) of not less than

90% is preferable, more preferably in enantiomer excess of an (R)-As an optically active form, isomer represented by the formula: not less than 99%.

wherein each symbol is as defined above, is preferable.

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example, JP-A 2002-187890, WO 02/30920 and the like, or analogous methods thereto. Further, the optically active optical resolution microorganism or enzyme, and the like) and an asymmetric oxidation method, etc. As the PPI of other benzimidazole using by known methods ţ disclosed in, a method applied method, can pe a clastereomer method, compound (III) can be produced (a fractional recrystallization per se, and are produced by the methods obtained by invention compound disclosed in WO 03/27098. can be derivative, the present (III) column method, compound nethods

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active ingredient represented by the general formulae  $(\mathrm{I}')$ ,  $(\mathrm{I})$ , differ the present invention compounding amounts of the in nseq Although the and (III) (II)

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by weight to about 40% by weight. When the active lansoprazole, the amount is about 8% by weight to about 40% amounts are, for example, about 1% by weight to about granules of the present invention, preferably about 1% by weight to about 50% by weight and further preferably about in particular depending on the kinds and doses of the active ingredient, on the total amount of tablets ingredient is a benzimidazole compound P?I, based weight by weight. γq

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wherein the active ingredient is released with prolonged properties and conditions respectively. Further, 2 kinds of these release-controlled coating-layers may be stacked in 2 and (III), 2 kinds or more of a tablet, granule or fine 2 kinds of granules such as granules wherein the active ingredient is released comparatively quickly and granules general active compound thereof (R-isomer and the like) and the granule having different behavior of release (for example, releaserelease or more layers in the respective granules or fine granules. imidazole derivative PPI represented by the formula (II) In case of capsules containing the imidazole PPI, the The preparation which enhances blood levels at different or an using рà especially benzimidazole PPI represented as lansoprazole combination, controlled coating-layers which have 넊 (I) such filled or **.**0 (I') тау formula time) 2 15 25 20

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earlier stage after administration to reveal drug efficacy the expression of the which contains a granule having an intermediate layer on the core particle containing the above-mentioned active intermediate layer (accordingly, among the above-mentioned the release of active controlled coating-layers of the present invention and the administering capsules containing a tablet, granule or fine the present invention and the digestive tract retentive gel-forming preparation containing only granules having a usual enteric coat. Further, when the controlling function, the capsules of the present invention þe release-controlled granule or fine granule by the present the releasemay not always contain the gel-forming polymer. Capsules by preparing a preparation (preferably a capsule) or by small size tablet is preferable), or fine granule to be filled has an enough releaseprepared using only the release-controlled tablet, combining the releaseţ can 6 ingredient is comparatively rapid.), in addition polymer; granule of enteric coat control layer of granule having release-controlled digestive tract retentive gel-forming and then sustain the drug efficacy by invention, the granule in which γ̈́ one layer or ø granule having the release fine granule, together with the (in this case, ingredient and only or οĘ fine granule efficacy or polymer, provided, granule þe tablet tablet,

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releasing type granule having only enteric coat. In case of there can be prepared the preparations by which the blood level is preferably enhanced at a more earlier stage to achieve drug efficacy and to reach the first maximal blood and then the second maximal blood level is reached by the release of active ingredient from granule's in which expressed. Further, the controlled release preparation such capsule of the capsule wherein the active may be or at an interval. A high maintained over a two peaks are controlled tablet, granule or fine granule with a fastadministration, quickly the above-mentioned controlled release combined release was controlled, that is, long time by such combined administration. released blood level of active ingredient can be preparations and present invention and a usual ingredient is comparatively administered at the same time such combined

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Usual enteric-coaled Granules can be produced, for example, according to the method described in JP-A 63-301826. Further, it is preferable to prepare a stabilized preparation according to the method described in JP-A 62-277322.

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Further, the granule which contains lansoprazole or optically active form thereof and the like at a higher concentration and is sufficiently stabilized can be produced as follow. Namely, there are produced the granules

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to about 40% by weight of lansoprazole and the like based as a stabilizer and average particle diameter is about to about 2500 µm, using known granulation methods (for an intermediate layer wherein on the total amount of the granule and a basic inorganic a fluidized enteric weight such as a fluid-bed granulation method (for example, granulation method and a stirring granulation method said active ingredient layer contains about 10% by an layer, example, a fluid-bed fluidized granulation method) and centrifugal fluid-bed granulation method), intermediate layer an active ingredient layer, said active ingredient said ö formed coated layer ő Ē. formed 009

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Specifically, the active ingredient layer can be obtained, for example, by coating a core particle with a dusting powder containing the imidazole PPI, a basic metal while spraying a binding solution such as hydroxypropylcellulose the like on the core particle. As said core particle, example, Nonpareil prepared by coating sucrose (75 parts by weight) with corn starch (25 parts by weight) by a granule using Further, a core granule itself may be the above-mentioned of are exemplified. drug. The average particle size like the a spherical core an excipient, a disintegrant and the like crystalline cellulose and known method per se, οĘ active ingredient for

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a spherically granulated product of are of product of product like the a spherically granulated spherically granulated and lactose and cellulose ø cellulose, starch, core, the sucrose and crystalline crystalline exemplified. As

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of core, and preferably about 0.1 part by weight to about 5 The ratio of coating layer relative to the core can be particle size of granules. For example, it is usually about 0.2 part by weight to about 5 parts by weight based on 1 part by weight selected within a range of being able to control elution property of active ingredient and the parts by weight.

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Then, the intermediate layer is formed on the active Examples of the intermediate layer include, for example, a example, the component of the intermediate layer is diluted At this time, it is preferable to coat the layer while layer in which sugars such as sucrose (purified white sugar the mixture is honey and sugar alcohol (D-mannitol, erythritol and the ingredient layer obtained by a conventional method. For sprayed in liquid form to coat the active ingredient layer. spraying a binding agent such as hydroxypropylcellulose. (those pulverized (powder sugar) and those not pulverized) and the like), starch sugar such as corn starch, lactose, polymeric compounded with with purified water and the like, and appropriately like)

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are

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said granules is 14 to 80 mesh in general.

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prepare a preparation may be further appropriately added in and the like)) and antistatic agents t t Excipients (for example, masking agent materials such as low substituted hydroxypropylcellulose, hydroxypropyl methylcellulose (for pyrrolidone, hydroxyethyl (titanium oxide, talc and the like) which are added polyvinyl polyvinyl alcohol, methylcellulose and the intermediate coating layer, if necessary. the like), hydroxypropylcellulose, and oxide methylcellulose. TC-5 (titanium example,

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The coat amount of the intermediate coating layer is usually, for example, about 0.02 part by weight to about 1.5 parts by weight based on 1 part by weight of granules containing the benzimidazole PPI, and preferably about 0.05 part by weight to about 1 part by weight.

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granules which contain lansoprazole and stabilized can be produced by forming a enteric coated for enteric polymer base materials such as cellulose acetate chloride copolymer (Eudragit RS or RL; manufactured by Rohm sufficiently as aqueous nydroxymethylcellulose acetate succinate, ethyl acrylatemethacrylate layer on the intermediate coating layer by a conventional phthalate (CAP), hydroxypropyl methylcellulose phthalate, of the enteric coated layer, example, sustained release base materials such are methacrylate-trimethylammoniumethyl a high concentration and As the component the the like at Further, method. methyl

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the like), acetylated monoglyceride, triacetin and castor These may be used alone or by mixing 2 kinds manufactured by Rohm Co.), carboxymethyl polyethyiene glycol (polyethylene glycol 6000 (trade name: Macrogol 6000, and copolymer wateras such acrylate plasticizers soluble polymer, triethyl citrate, methacrylate-ethyl ethylcellulose and shellac; (Eudragit NE30D; methyl oil are used. more.

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The coat amount of the enteric coated layer is about 10% by weight to about 70% by weight based on the total amount of granules before enteric coating, preferably about 10% by weight to about 50% by weight and more preferably about 15% by weight to about 30% by weight.

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In case of a tablet, for example, the benzimidazole compound, an excipient, a binding agent, a disintegrant, a lubricant and the like are mixed to directly produce tables by compression, or the granules which is produced in same manner as the above-mentioned granules can be compressed into tablet. Further, alternatively, 2 layered tablets may be prepared with a commercially available multilayer tablet machine using the granulated granules.

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Among the preparations of the present invention, preparations containing the PPI of benzimidazole compound represented by the general formula (I') such as lansoprazole and optically active form thereof, above all

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juice the present invention or a salt thereof is less toxic, and 9 and secretion suppressing effect is rapidly expressed, and since it is gradually converted to its original compound in vivo, it has a sustainability and is useful as anti-ulcer compound of compound (I') of and the like in vivo, and are useful as a medicine because the imidazole is stable to an acid, it is unnecessary to prepare an cost of preparing enteric preparations is reduced, and the patients the a prodrug-type imidazole compound derivative (in particular, a compound represented mucosa protective effect, anti-Helicobacter pylori effect compound represented by the above-mentioned general formula the absorption general an optically active compound thereof) have superior antiulcer effect, gastric juice secretion suppressing effect, be orally or parenterally (for example, local, rectal, vein administration) and safely administered as it is or with weak deglutition, in particular, aged people and (III) ğ gastric the the because the size administration, compound represented by (II) preparations becomes small. Further, since of low toxicity. In particular, since preparations, by the above-mentioned general formula oŧ dosed agents and the like. The PPI enteric preparation for oral PPI enteric the children are easily and faster than PPI benzimidazole formula (I), (II) is

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pharmacologically acceptable carrier according to a known method per se, that is, for example, as a preparation such as a tablet (including sugar coated tablet and film coated tablet), powder, granule, capsule (including soft capsule), intraoral disintegrating tablet, liquid, injection, suppository, sustained-release agent and liniment.

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nanagement after operation and by cerebro-vascular accident, gastric ulcer, duodenum ulcer, (Non Ulcer Dyspepsia), gastric cancer (including gastric οĘ stress ulcer and hemorrhagic gastritis; the suppression of prevention of 1), gastric MALT lymphoma and the like; the eradication of upper digestive acute upper digestive tract hemorrhage caused by invasive stress (stress caused by major operation which requires intensive present cat, rabbit, yastritis, reflux esophagitis, Symptomatic Gastroesophageal Reflux Disease (symptomatic GERD) with no esophagitis, NUD interleukin-1β caused by gene polymorphism of interleukinmarginal ulcer and the like), Zollinger-Ellison syndrome, promotion mammals ulcer, granule or fine granule of the example, human, monkey, sheep, horse, dog, mouse and the like) for the treatment and the digestive production administrated to felicobacter pylori, the suppression of the digestive ulcer (for example, hemorrhage caused by be orally accompanied with tablet, invention can tract

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head lesion, multiorgan disorder and wide range burn which

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with

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composition

pharmaceutical

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prevention of hyperchylia and ulcers caused The granules and capsules of the present invention may be used in combination with ingredients) for the eradication of Helicobacter pylori and require intensive care), and the treatment and prevention steroid anti-inflammatories; the to 3 active other active ingredients (for example, 1 122 by stress after operation, etc. of ulcer caused by non treatment and

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for example, an antibacterial such as an anti-Helicobacter granules and capsules of the present invention with the antibacterials Among these, the combination with an an anti-Helicobacter pylori active Examples of the anti-Helicobacter pylori active substance amoxicillin, benzylpenicillin, piperacillin, mecillinam and cephachlor and the like), macrolide antibiotic (for example, and preferable. like), In particular, include, for example, penicillin antibiotic (for example, Examples of the "other active ingredients" include, cefixime, example, an imidazole compound and as erythromycin the antibiotic (for example, tetracycline, minocycline, streptomycin and r, the compound salts. pharmaceuticals obtained by combining (for bismuth such antibiotic clarithromycin), tetracycline imidazole pylori active substance, erythromycin antibiotic quinolone compound, and antibacterial such as the like), cephem aп are preferable. substance and

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like gentamicin, particular, the and H example, penicillin antibiotic, macrolide antibiotic etc. imipenem (for antibiotic the like), uninoglycoside amikacin and preferred. are

also umoxicillin and the like) and/or erythromycin antibiotic example, metronidazole, miconazole and the like. Examples there are preferable, and for example, ofloxacin, ciproxacin and the Examples of the "imidazole compound" include, for mentioned bismuth acetate, bismuth citrate and the like. invention example, preferable for i.s compound" present penicillin antibiotic (for the ''like) example, it is use the granules and capsules of the Źor "quinolone In particular, clarithromycin and eradication of Helicobacter pylori. include, The antibacterial of salt" exemplified. "bismuth together with example, like are the (for oŧ വ 10 15

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high been often filled in No.3 capsules, and capsules containing concentration are unexpectedly obtained by providing an intermediate coating layer, compounding a basic inorganic particle size granules without damaging the stability of the active 30 mg have been often filled in No.1 capsules. However, the capsules containing 15 mg of crystalline lansoprazole have lansoprazole, at ingredient of salt stabilizer and further controlling the example, in case containing an active Further, for granules οĘ

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Ç рe Thus, since the amount of components other than the active ingredient can be reduced, No. 4 can ţ шg be miniaturized 30 No.5 capsules and capsules containing miniaturized to No.3 to No.5 capsules. can ingredient and preparation. шd 15 capsules containing

the Further, No.1 to No.3 capsule can be also used for capsule containing 60 mg

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Further, in case of the optically active compound of lansoprazole, No.3 to No.5 capsule, No.2 to No.4 capsule capsule the containing 30 mg, 40 mg and 60 mg respectively. used for рę. can No.1 to No.3 capsule and

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mg of lansoprazole or lansoprazole R-isomer contains the active ingredient at high concentration and the capsule is miniaturized, it is easy to take and suitable for treatment acid excessive secretion symptom including Zollinger-For example, since the capsule containing 60 Ellison syndrome in particular. oŧ

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οĘ οĘ active ingredient and the like, and are not specifically 0.5 to 1500 mg/day and preferably about 5 to 150 mg/day as These preparations containing these symptom, age for administration objective, sexuality, body limited. For example, when the drug is orally administrated to adults (60 kg) as an anti-ulcer agent, the dose is about kind Dose per day differs depending on the extent the of administration, interval, active ingredient. weight, timing

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t t divided þe benzimidazole or imidazole compound may

administer once a day or 2 to 3 times a day

replaced with gas other than oxygen), vacuum package and pharmaceutical solid preparation is packed with an oxygen Further, the form of package may be also stabilized in order to improve the stability of the solid preparation of preparation present invention can be improved by using package form package suppressing the permeation of oxygen and gas (namely, package The stabilization is improved by reducing oxygen amount with which the solid preparation is directly brought in contact, using these рe another packing may of the present invention at storage or transportation. enclosed, containing the benzimidazole or imidazole compound capsule 13 deoxidizer the carried out together with the package. package enclosed with a deoxidizer. package replaced with permeating material, and then οĘ the stabilization When forms. moisture, example, such as package Ŋ 15 10

## Examples 20

present invention is explained in detail in the The present following by referring to Reference Examples, Synthetic Examples, Examples and Experiment Examples. invention is not limited by the Examples.

The corn starch, hydroxypropyl cellulose (HPC-L),

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polyethylene glycol 6000 and titanium oxide used in the materials to the 14th revised Japanese Pharmacopoeia. following Examples of Preparation are the conformed

H-NMR spectra were determined with CDC13, DMSO-d, and CD3OD data are shown in chemical shift  $\delta$  (ppm) from the internal as the solvent using Varian Gemini-200 and Mercury-300; In the following Reference Examples and Synchetic Examples, room temperature means about 15-30°C. standard tetramethylsilane.

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Other symbols in the present specification mean the following.

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s: singlet

d: doublet

t: triplet

q: quartet

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m: multiplet

br: broad

bs: broad singlet

bm: broad multiplet

coupling constant <del>ن</del>ا

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Reference Example 1

tert-Butyl 2-hydroxyethyl (methyl) carbamate

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2 hrs., the mixture was concentrated under reduced pressure with water (100 mL) and dried over anhydrous magnesium The residue was dissolved in ethyl acetate (150 mL), washed sulfate. Concentration under reduced pressure gave the under ice-cooling. After stirring at room temperature for ethyl acetate (90 mL) was dropwise added a mixture of dicert-butyl dicarbonate (87.30 g) and ethyl acetate (10 mL) To a mixture of 2-(methylamino)ethanol (30.04 g)

H-NMR(CDCl3): 1.47(9H,8), 2.92(3H,8), 3.40(2H,t,J=5.1Hz),

title compound (66.19 g) as a colorless oil.

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3.72-3.80(2H;m).

Reference Example 2

2-(Methylamino)ethyl acetate hydrochloride

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To a mixture of 2-(methylamino) ethano. (1.50 g) and ethyl acetate (20 mL) was added di-tert-butyl dicarbonate cooling for 1.5 hrs., acetic anhydride (2.08 mL), pyridine After stirring at room temperature for 2 hrs., ethyl (4.37 g) under ice-cooling. After stirring under ice- $(1.78~{\rm mL})$  and 4-dimethylaminopyridine  $(0.12~{\rm g})$  were added.

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acetate (50 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL), a 5% agueous citric drying over anhydrous magnesium sulfate, the mixture was To the residue was added a 4N hydrogen chloride - ethyl acetate solution (20 hrs. Diethyl ether (10 mL) was added, and the precipitated solid was collected by filtration. The solid was dried After under reduced pressure to give the title compound (2.93 g) mL), and the mixture was stirred at room temperature for acid solution (50 mL) and saturated brine (50 mL). concentrated under reduced pressure. as a white solid.

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H-NMR(DMSO-de): 2.07(3H,s), 2.53(3H,s), 3.12-3.17(2H,m),4.24-4.30(2H,m), 9.29(2H,br).

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Reference Example 3

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2-(Methylamino)ethyl trimethylacetate hydrochloride

2 Reference Example 1 and ethyl acetate (15 mL) was added triethylamine (1.67 mL) and a mixture of trimethylacetyl chloride (1.35 mL), and ethyl acetate (5 mL) was dropwise 2 hrs., pyridine (1.62 mL) was added, and the mixture was stirred obtained tert-butyl After stirring at room temperature for g (1.75)οţ hydroxyethyl (methyl) carbamate mixture added.

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overnight, at room temperature. Ethyl acetate (50 mL) was and the mixture was washed with water (50 mL), a 5% aqueous citric acid solution (50 added to the reaction mixture,

ML) and saturated brine (50 mL), and dried over anhydrous

The solid was dried under reduced pressure to give the After concentration under reduced pressure, a 4N hydrogen chloride - ethyl acetate solution After stirring at room temperature for 2 hrs., diethyl ether (10 mL) was added, and the precipitated solid was collected by filtration. title compound (1.65 g) as a white solid. (10 mL) was added to the residue. magnesium sulfate. S 5

H-NMR(DMSO-d6): 1.18(9H,s), 2.56(3H,s),

3.17(2H,t,J=13.5Hz), 4.22"4.28(2H,m), 9.19(2H,br) Reference Example 4

2-(Methylamino)ethyl cyclohexanecarboxylate hydrochloride

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To a mixture of tert-butyl 2-hydroxyethyl

and ethyl acetate (20 mL) were added pyridine (0.97 mL) and (methyl) carbamate (1.75.g) obtained in Reference Example 1 syclohexanecarbonyl chloride (1.60 mL) was dropwise added. 4-dimethylaminopyridine (catalytic amount), and

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was dried under reduced pressure to give the title compound reaction mixture, and the mixture was washed with water  $\langle 50 \rangle$ saturated brine (50 mL), and dried over anhydrous magnesium 4<u>N</u> The solid added to the residue. After stirring at room temperature (0.65 mL) and cyclohexanecarbonyl chloride (0.58 mL) were After stirring at room temperature for 2 hrs., pyridine hydrogen chloride - ethyl acetate solution (10 mL) was sulfate. After concentration under reduced pressure, for 2 hrs., diethyl ether (10 ml) was added, and the Ethyl acetate (50 mL) was added to the and the mixture was stirred overnight at room ml), a 5% agueous citric acid solution (50 mL) and precipitated solid was collected by filtration. (1.98 g) as a white solid. temperature.

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<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.10-1.45(5H,m), 1.54-1.73(3H,m), 1.83-1.93(2H,m), 2.29-2.42(1H,m), 2.54(3H,s), 3.12-3.18(2H,m), 4.23-4.29(2H,m), 9.23(2H,br).

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Reference Example 5

2-(Methylamino)ethyl benzoate hydrochloride

To a mixture of 2-(methylamino)ethanol (30.04 g) and ethyl acetate (90 mL) was dropwise added a mixture of ditext-butyl dicarbonate (87.30 g) and ethyl acetate (10 mL)

was washed with ethyl acetate (100 mL) and the filtrate and anhydrous magnesium sulfate, the mixture was concentrated room The solid che washing were combined, wnich was washed with water (100 under reduced pressure. The residue was dissolved in ethyl under ice-cooling. After stirring at room temperature for g) and pyridine (38.8 mL) After drying at stirring temperature for 1 hr., a solid was filtered off. After and saturated brine (100 mL). 1 hr., benzoyl chloride (61.8 were added under ice-cooling. 10

acetate (100 mL), a 4N hydrogen chloride - ethyl acetate solution (200 mL) was added, and the mixture was stirred at room temperature for 30 min. Diethyl ether (100 mL) was added and a solid was collected by filtration. The solid was washed twice with ethyl acetate (100 mL) and dried was washed twice with ethyl acetate (100 mL) and dried

under reduced pressure at  $60^{\circ}\text{C}$  to give the title compound (57.4 g) as a white solid.

H-NMR(DMSO-ds): 2.62(3H,s), 3.32(2H,m),

1.53(2H,t,J=9.9Hz), 7.51-7.57(2H,m), 7.68(1H,m),

8.11(2H, d, J=7.8Hz), 9.26(2H, bs)

20 Reference Example 6

2- (Methylamino) ethyl 4-methoxybenzoate hydrochloride

To a mixture of tert-butyl 2-hydroxyethyl

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H<sub>3</sub>C H

chloride (1.88 g) and pyridine (0.97 mL). After stirring at room temperature for 14 hrs., 4-methoxybenzoyl chloride (0.70 g) and pyridine (0.97 mL) were added and the mixture was stirred at room temperature for 1 hr. Ethyl acetate (80 mL) was added to the reaction mixture, and the mixture

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(methyl)carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (10 mL) were added 4-methoxybenzoyl

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To a mixture of tert-butyl 2-hydroxyethyl

(methyl)carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (10 mL) were added 3-chlorobenzoyl

was washed with water (20 mL), a saturated agueous sodium hydrogen carbonate solution (20 mL) and water (20 mL), and

- chloride (1.92 g) and pyridine (0.97 mL). After stirring at room temperature for 1 hr., the mixture was stirred at 60°C for 6 hrs. Ethyl acetate (80 mL) was added to the reaction mixture, and the mixture was washed with water (20 mL), a saturated aqueous sodium hydrogen carbonate solution
- magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen chloride ethyl acetate solution (10 mL) was added to the residue. After stirring at room temperature for 22 hrs., diethyl ether (15 mL) was added,

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After

a 4N hydrogen

and

dissolved in ethyl acetate (10 mL),

After

concentration under reduced pressure, the residue was

dried over anhydrous magnesium sulfate.

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stirring at room temperature for 1 hr., diethyl ether (20

chloride - ethyl acetate solution (10 mL) was added.

mL), was added, and the precipitated solid was collected by

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and the precipitated solid was collected by filtration. The solid was washed twice with ethyl acetate (15 mL) and dried under reduced pressure at 60°C to give the title compound (2.01 g) as a white solid.

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(15 mL) and dried under reduced pressure at 60°C to give

the title compound (1.99 g) as a white solid.

'H-NMR(DMSO-d<sub>6</sub>): 2.62(3H,s), 3.32(2E,m),

4.48(2H,t,J=5.0Hz), 7.07(2H,d,J=8.7Hz), 8.06(2H,d,J=8.7Hz),

2-(Methylamino)ethyl 3-chlorobenzoate hydrochloride

Reference Example 7

9.04(2H,bs).

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filtration. The solid was washed twice with ethyl acetate

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.63(3H,s), 3.32(2H,m),

20 4.53(2H,t,J=4.9Hz), 7.60(lH,t,J=8.0Hz), 7.78(lH,d,J=8.0Hz), 8.05(lH,d,J=8.0Hz), 8.15(lH,s), 9.07(2H,bs).

Reference Example 8

2-(Methylamino)ethyl 3,4-difluorobenzoate

hydrochloride

To a mixture of tert-butyl 2-

S

residue. After stirring at room temperature for 4 hrs, the chloride - ethyl acetate solution (10 mL) was added to the mixture was washed with water  $(20~\mathrm{mL})$ , a saturated aqueous mL). After stirring at room temperature for 3 days, ethyl under reduced pressure at  $60^{\circ}\text{C}$  to give the title compound residue was washed with ethyl acetate (15 mL), and dried sodium hydrogen carbonate solution (20  $\pi L$ ) and water (20 Reference Example 1 and ethy] acetate (10 mL) were added 3,4-difluorobenzoyl chloride (1.77 g) and pyridine (0.97 mL), and dried over anhydrous magnesium sulfate. After The mixture was concentrated under reduced pressure. The concentration under reduced pressure, a 4N hydrogen acetate (80 mL) was added to the reaction mixture. hydroxyethyl (methyl) carbamate (1.75 g) obtained in (2.05 g) as a white solid.

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H-NMR(DMSO-d6): 2.62(3H,s), 3.32(2H,m), 20

4.53(2H,t,J=5.0Hz), 7.64(1H,m), 8.00(1H,m), 8.25(1H,m),

9.25(2H,bs).

Reference Example

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2-(Methylamino)ethyl 4-trifluoromethoxybenzoate

hydrochloride

To a mixture of tert-butyl 2-hydroxyethyl

(methyl)carbamate (1.30 g) obtained in Reference Example 1 and ethyl acetate (10 mL) were added 4-S

crifluoromethoxybenzoyl chloride (1.83 g) and pyridine (0.72 mL). The mixture was stirred at 60°C for 25 hrs. Ethyl acetate (60 mL) was added to the reaction mixture,

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and the mixture was washed with water (30 mL), a saturated chloride - ethyl acetate solution (10 mL) was added to the water (20 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen aqueous sodium hydrogen carbonate solution (20 mL) and

residue. After stirring at room temperature for 14.5 hrs., the mixture was concentrated under reduced pressure. The residue was washed twice with ethyl acetate (15 mL), and dried under reduced pressure at 60°C to give the title compound (1.83 g) as a white solid.

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'H-NMR(DMSO-ds): 2.63(3H,s), 3.31(ZH,m), 20

..54(2H,t,J=4.9Hz); 7.55(2H,d,J=8.5Hz), 8.24(2H,d,J=8.5Hz)

9.02(2H,bs).

Reference Example 10

136

2-(Methylamino)ethyl 4-fluorobenzoate hydrochloride

To a mixture of tert-butyl 2-hydroxyethyl

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stirred at room temperature for 6.5 hrs. Ethyl acetate (80 methyl)carbamate (1.75 g) obtained in Reference Example 1 chloride (1.74 g) and pyridine (0.97 mL). The mixture was nL) was added to the reaction mixture, and the mixture was hydrogen carbonate solution (3C mL), water (30 mL) and washed with water (30 mL), a saturated aqueous sodium and ethyl acetate (10 mL) were added 4-fluorobenzoyl

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saturated brine (30 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N filtration. The solid was washed twice with ethyl acetate added to the residue. After stirring at room temperature (15 mL) and dried under reduced pressure at 60°C to give hydrogen chloride - ethyl acetate solution (10 mL) was for 1 hr., the precipitated solid was collected by the title compound (1.89 g) as a white solid. 15

 $^{1}$ H-NMR(DMSO-d<sub>6</sub>): 2.62(3H,s), 3.32(2H,m),

4.52(2H,t,J=4.9Hz), 7.34-7.44(2H,m), 8.16-8.24(2H,m), 20

Reference Example 11

9.18(2H, bs).

2-(Methylamino)ethyl 3,4,5-trimethoxybenzoate

137

hydrochloride

To a mixture of tert-butyl 2-hydroxyethyl

chloride (1.30 g), pyridine (0.97 mL) and ethyl acetate (10 After stirring at 60°C for 14 hrs., 3,4,5-trimethoxybenzoyl (methy1) carbamate (1.75 g) obtained in Reference Example 1 trimethoxybenzoyl chloride (2.54 g) and pyridine (0.97 mL) mL) were added, and the mixture was stirred at 60°C for 24 hrs. The reaction mixture was filtered and ethyl acetate and ethyl acetate (10 mL) were added 3,4,5-

hydrochloric acid (30 mL), water (30 mL), an aqueous copper After partitioning, ethyl acetate layer was washed with 1N (50 mL) and water (30 mL) were added to the filtrate.

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After concentration under reduced pressure, the residue was (II) sulfate solution (30 mL), water (30 mL) and saturated acetate solution (10 mL) was added to the purified product ethyl acetate:hexane=1:1). A 4N hydrogen chloride - ethyl brine (30 ml), and dried over anhydrous magnesium sulfate. purified by silica gel column chromatography (eluted with

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After stirring at room temperature for 4 hrs, the mixture was concentrated under reduced pressure. Toluene (10mL)

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(15 mL), the solid was dried under reduced pressure to give After washing with ethyl acetate pressure. The residue was suspended in ethyl acetate, and was added, and the mixture was concentrated under reduced the title compound (1.79 g) as a white solid. the solid was filtrated.

'H-NMR(DMSO-d6): 2.61(3H,s), 3.28-3.35(2H,m), 3.74(3H,s), 3.87(6H,s), 4.48-4.54(2H,m), 7.40(2H,s), 9.43(2H,br).

2- (Methylamino) ethyl 2-pyridinecarboxylate

Reference Example 12

dihydrochloride 10

pyridine (1.21 mL) and 4-dimethylaminopyridine (3.122 g) in methy1) carbamate (1.75 g) obtained in Reference Example 1, successively with a 5% aqueous copper (II) sulfate solution cetrahydrofuran was dropwise added triethylamine (2.09 mL) reaction mixture and the mixture was extracted with ethyl To a solution (100 mL) of tert-butyl 2-hydroxyethyl dried over anhydrous sodium sulfate and evaporated under Water (200 mL) was added to the under ice-cooling, and the mixture was stirred at room (100 mL), water (100 mL) and saturated brine (100 mL), 2-pyridinecarbonyl chloride hydrochloride (2.67 g), acetate (150 mL). The organic layer was washed temperature for 6 hrs.

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acetate (50 mL) and ethanol (100 mL), and a 4N hydrogen reduced pressure. The residue was dissolved in ethyl

swice with ethyl acetate (100 mL), and dried under reduced mixture was stirred at room temperature for 1 hr. The precipitated solid was collected by filtration, washed pressure at 60°C to give the title compound (1:08 g) chloride - ethyl acetate solution (15 mL) was added. white solid. വ

8.18(1H,m), 8.36-8.40(1E,m), 8.70-8.9C(1H,m), 9.48(2H,br). 1.63(2H,t,J=5.0Hz), 5.26(1H,bs), 7.77-7.84(1H,m), 8.14-H-NMR(DMSO-ds): 2.62(3H,t,J=5.4Hz), 3.35(2H,m), Reference Example 13

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2-(Methylamino)ethyl methoxyacetate

and ethyl acetate (10 mL) were added methoxyacetyl chloride methyl) carbamate (1.75 g) obtained in Reference Example 1 was added to (1.20 g) and pyridine (0.97 mL). After stirring at room the reaction mixture. The mixture was washed with water After concentration under (20 mL), a saturated aqueous sodium hydrogen carbonate reduced pressure, the residue was dissolved in ethyl solution (20 mL) and water (20 mL), and dried over To a mixture of tert-butyl 2-hydroxyethyl temperature for 3 hrs., ethyl acetate (70 mL) anhydrous magnesium sulfate. 15 20

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acetate (5 mL), and a 4N hydrogen chloride - ethyl acetate solution (10 mL) was added. After stirring at room temperature for 1 hr., the mixture was concentrated under reduced pressure. Water (60 mL) and diethyl ether (30 mL) were added to the residue. After stirring, the aqueous layer was separated and taken. The aqueous layer was basified with sodium hydrogen carbonate and extracted twice with ethyl acetate (40 mL). The ethyl acetate layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (1.00 g) as a colorless oil.

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'H-NMR(CDC13): 2.40(1H,bs), 3.06(3H,s), 3.44(3H,s),

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3.57(2H,t,J=5.1Hz), 3.75-3.82(2H,m), 4.13(2H,s).

Reference Example 14

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Ethyl 2-(methylamino)ethyl carbonate hydrochloride H  $_{3}^{0}$   $_{0}^{0}$   $_{0}^{0}$   $_{0}^{0}$   $_{0}^{0}$ 

To a mixture of tert-butyl 2-hydroxyethyl (methyl) carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (20 mL) were added pyridine (0.97 mL) and 4-dimethylaminopyridine (catalytic amount), and ethyl chlorocarbonate (1.25 mL) was dropwise added. The mixture was stirred overnight at room temperature and ethyl acetate (50 mL) was added. The mixture was washed with water (50

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mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen chloride - ethyl acetate solution (10 mL) was

added to the residue. After stirring at room temperature for 2 hrs., diethyl ether (10 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (1.66 g) as a white solid.

10 'H-NMR(DMSO-d<sub>6</sub>): 1.23(3H,t,J=7.1Hz), 2.54(3H,s), 3.16-3.22(2H,m), 4.15(2H,q,J=7.1Hz), 4.32-4.37(2H,m),

9.25(2H,br). Reference Example 15 Isopropyl 2-(methylamino)ethyl carbonate hydrochloride

To a mixture of tert-butyl 2-hydroxyethyl

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(methyl)carbamate (3.50 g) obtained in Reference Example 1
and ethyl acetate (20 mL) were added isopropyl
chlorocarbonate (1.35 g) and pyridine (1.94 mL) urder icecooling. After stirring under ice-cooling for 3.5 hrs.,
isopropyl chlorocarbonate (1.84 g) was added, and the
mixture was stirred at room temperature for 2.5 hrs. Ethyl
acetate (120 mL) was added to the reaction mixture, and the

mixture was washed with water (50 mL) and saturated brine (50 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen chloride - ethyl acetate solution (10 mL) was added to the residue. After stirring at room temperature for 2 hrs., the precipitated solid was collected by filtration. The solid was washed with ethyl acetate (15 mL), and dried under reduced pressure at 60°C to give the title compound (1.38 g) as a white solid.

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<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.25(6H, d, J=6.2Hz), 2.56(3H,s), 3.20(2H,t,J=5.1Hz), 4.32(2H,t,J=5.1Hz), 4.80(1H,m),

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3.20(ZH, t, 0=3.1HZ), 4.3Z(ZH, t, 0=3.1HZ), 4.8U(

8.95(2H,bs).

Reference Example :6
Benzyl 2-(methylamino)ethyl carbonate hydrochloride

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To a mixture of tert-butyl 2-hydroxyethyl (methyl) carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (20 mL) were added pyridine (0.97 mL) and 4-dimethylaminopyridine (catalytic amount), and benzyl chlorocarbonate (1.57 mL) was dropwise added. After stirring at room temperature for 2 hrs., pyridine (0.65 mL) and benzyl chlorocarbonate (1.28 mL) were added. After stirring at room temperature for 5 days, pyridine (0.81 mL)

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was added under ice-cooling and a solution (5 mL) of benzyl chlorocarbonate (1.43 mL) in ethyl acetate was dropwise

added slowly. After stirring at room temperature for hrs., etnyl acetate (50 mL) was added to the mixture,

washed with water (50 mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, a 4N hydrogen chloride - ethylacetate solution (10 mL) was added to the residue. After

stirring at room temperature for 2 hrs., diethyl ether (10 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (1.99 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.55(3H,s), 3.21(2H,t,J=5.1Hz),

4.37(2H,t,J=5.1Hz), 5.18(2H,s), 7.30÷7.50(5H,m), 9.07(2H,br).

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Reference Example 17

2-(Methylamino)ethyl tetrahydropyran-4-yl carbonate hydrochloride

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To a solution (40 mL) of bis(trichloromethyl)carbonate (2.97 g) in tetrahydrofuran was dropwise added a solution

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saturated brine (50 mL), and dried over anhydrous magnesium (10 mL) of pyridine (2.43 mL) in tetrahydrofuran under ice-The ethyl tetrahydrofuran was dropwise added slowly. After stirring concentrated under reduced pressure, and ethyl acetate (50 hydrochloric acid (20 mL) and saturated brine (50 mL), and After concentration under reduced pressure, the Reference Example 1 and tetrahydrofuran (20 mJ) was added mixture was stirred overnight at room temperature. After washed with a 5% aqueous citric acid solution (50 mL) and 2 acetate layer was separated and taken, washed with 0.2N After stirring under ice-cooling for 10 min., tetrahydropyran-4-yl chlorocarbonate (1.53 g) obtained extracted with ethyl acetate (50 mL). The residue was dried over anhydrous magnesium sulfate. Concentration chlorocarbonate (1.53 g). To a mixture of tert-butyl 끉 above in tetrahydrofuran was dropwise added, and the concentration of the reaction mixture under reduced hydroxyethyl(methyl)carbamate (1.40 g) obtained in pressure, water (50 mL) was added, the mixture was of tetrahydropyran-4-ol (1.91 g) nL) and water (50 mL) were added to the residue. under reduced pressure gave tetrahydropyran-4-yl at room temperature for 2 hrs., the mixture was pyridine (0.78 mL), and a solution (10 mL) of solution (20 mL) sulfate.

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ether (2 mL), and a 4N hydrogen chloride - ethyl acetate obtained colorless oil (2.03 g) was dissolved in diethyl (eluted with ethyl acetate:hexane=4:1, then 3:2). The solution (5 mi) was added. After stirring at room

solid was collected by filtration and dried under reduced and the mixture was stirred overnight. The precipitated temperature for 30 min., diethyl ether (10 mL) was added pressure to give the title compound (1.20 g) as a white solid.

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2.54(3H,s), 3.2C(2H,m), 3.40-3.50(2H,m), 3.74-3.83(2H,m), 4.36(2H,t,J=5.1Hz), 4.72-4.83(1H,m), 9.32(2H,br). 'H-NMR(DMSO-d<sub>6</sub>): 1.50-1.65(2H,m), 1.87-1.98(2H,m), 10

Reference Example 18

2-Methoxyethyl 2- (methylamino) ethyl carbonate hydrochloride

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(methy1) carbamate (1.75 g) obtained in Reference Example 1 and ethyl acetate (20 mL) was added pyridine (1.62 mL) and a solution (5 mL) of 2-methoxyethyl chlorocarbonate (2.77 mixture was stirred overnight at room temperature. After g) in ethyl acetate was dropwise added slowly, and the concentration of the reaction mixture under reduced To a mixture of tert-butyl 2-hydroxyethyl

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residue was purified by silica gel column chromatography

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saturated brine (50 mL), and dried over anhydrous magnesium stirred overnight. The precipitated solid was collected by sulfate. After concentration under reduced pressure, the H-NMR(DMSO-d6): 2.54(3H,s), 3.19(2H,m), 3.26(3H,s), 3.52-3.57(2H,m), 4.20-4.25(2H,m), 4.33-4.39(2H,m), 9.26(2H,br) filtration, and dried under reduced pressure to give the washed with 5% aqueous citric acid solution (50 mL) and residue was dissolved in diethyl ether (2 mL), and a 4N After stirring at room temperature for 30 min., extracted with ethyl acetate (50 mL). The mixture was hydrogen chloride - ethyl acetate solution (5 mL) was diethyl ether (10 mL) was added, and the mixture was pressure, water (50 mL) was added, the mixture was title compound (1.56 g) as a white solid.

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tert-Butyl ethyl (2-hydroxyethyl) carbamate

Reference Example 19

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sthyl acetate (100 mL) was added di-tert-butyl dicarbonate To a mixture of 2-(ethylamino)ethanol (8.91 g) and temperature for 3 days, the mixture was washed with (21.8 g) under ice-cooling. After stirring at room saturated brine (100 mL), and dried over anhydrous

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give the title compound (1.54 g) as a white solid.

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3.27(2H,q,J=7.0Hz), 3.37(2H,t,J=5.2Hz), 3.73(2H,q,J=5.2Hz). magnesium sulfate. Concentration under reduced pressure gave the title compound (19.0 g) as a colorless oil. H-NMR(CDC13): 1.11(3H,t,J=7.0Hz), 1.47(9H,s),

2-(Ethylamino)ethyl acetate hydrochloride

Reference Example 20

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and the mixture was washed with water (50 mL), a 5% aqueous filtration. The solid was dried under reduced pressure to lfter drying over anhydrous magnesium sulfate, the mixture chloride - ethyl acetate solution (10 mL) was added to the for 1 hr. Ethyl acetate (10 mL) and diethyl ether (20 mL) citric acid solution (50  $\pm$ L) and saturated brine (50  $\pm$ L). residue, and the mixture was stirred at room temperature imethylaminopyridine (0.061 g). After stirring at room emperature for 3 hrs., ethyl acetate (50 mL) was added, was concentrated under reduced pressure. A 4N hydrogen were added, and the precipitated solid was collected by Example 19 and ethyl acetate (20 mL) were added acetic hydroxyethyl)carbamate (1.89 g) obtained in Reference unhydride (1.04 mL), pyridine (0.89 mL) and 4-To a mixture of tert-butyl ethyl (2-15 20 10

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H-NMR(DMSO-d6): 1.22(3H,t,J=7.3Hz), 2.07(3H,s),

2.95(2H,q,J=7.3Hz), 3.15(2II,t,J=5.3Hz), 4.24-4.30(2E,m),

9.17(2H, br)

Reference Example 21

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tert-Butyl 2-hydroxyethyl(isopropyl)carbamate

sulfate and concentrated under reduced pressure to give the added to the residue. The mixture was extracted with ethyl acetate (200 mL). The ethyl acetate layer was washed with concentrated under reduced pressure and water (100 mL) was dicarbonate (22.2 g), and the mixture was stirred at room To a solution (30 mL) of 2-(isopropylamino)ethanol saturated brine (100 mL), dried over anhydrous sodium (10.0 g) in tetrahydrofuran was added di-tert-butyl temperature for 1 hr. The reaction mixture was citle compound (21.21 g) as a colorless oil.

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H-NMR(CDC13): 1.12(6H, d, J=6.6Hz), 3.30(2H, t, J=5.0Hz),

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3.71(2H,t,J=5.0Hz), 3.80-4.30(1H,m).

Reference Example 22

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2-(Isopropylamino)ethyl acetate hydrochloride

The ethyl acetate layer was washed (isopropyl) carbamate (5.0 g) obtained in Reference Example acetic anhydride (2.79 mL) and the mixture was stirred at added to the residue, and the mixture was extracted with to a solution (15 mL) of tert-butyl 2-hydroxyethyl coom temperature for 18 hrs. The reaction mixture was concentrated under reduced pressure, water (50 mL) was 21 in tetrahydrofuran were added pyridine (6.0 mL) and ethyl acetate (100 mL).

pressure to give the title compound (3.14 g) as a colorless was stirred at room temperature for 1 hr. The precipitated chloride - ethyl acetate solution (10 mL), and the mixture solid was collected by filtration, and dried under reduced sulfate and concentrated under reduced pressure. The obtained colorless oil was dissolved in a 4N hydrogen saturated brine (50 mL), dried over anhydrous sodium with a 5% aqueous citric acid solution (50 mL) and

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H-NMR(DMSO-d6): 1.25(6H, d, J=6.6Hz), 2.08(3H, s), 3.10-

3.40(3H,m), 4.29(2H,t,J=6.0Hz), 9.11(2H,Dr). 20

Reference Example 23

Ethyl 2-(isopropylamino)ethyl carbonate hydrochloride

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pressure. The obtained colorless oil was dissolved in a 4N ethyl acetate (100 mL). The ethyl acetate layer was washed hydrogen chloride - ethyl acetate solution (10 mL), and the ethyl chlorocarbonate (2.81 mL) and the mixture was stirred isopropyl) carbamate (5.0 g) obtained in Reference Example concentrated under reduced pressure, and water (50 mL) was under reduced pressure to give the title compound (3.34 g) at room temperature for 18 hrs. The reaction mixture was added to the residue, and the mixture was extracted with precipitated solid was collected by filtration and dried To a solution (15 mL) of tert-butyl 2-hydroxyethyl 21 in tetrahydrofuran were added pyridine (6.0 ml) and sulfate and the mixture was concentrated under reduced mixture was stirred at room temperature for 1 hr. The saturated brine (50 mL), dried over anhydrous sodium with a 5% aqueous citric acid solution (50 mL) and as a colorless solid.

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H-NMR(DMSO-de): 1.20-1.30(9H,m), 3.10-3.40(3H,m),

4.17(2H,q,J=7.4Hz), 4.37(2H,t,J=5.6Hz), 9.13(2H,br). 20

Reference Example 24

cert-Butyl cyclohexyl(2-hydroxyethyl)carbamate

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pressure. The residue was dissolved in ethyl acetate (200 dicarbonate (21.8 g). After stirring at room temperature To a solution (200 mL) of 2-(cyclohexylamino)ethanol mL), washed with water (100 mL) and saturated brine (100 for 2 days, the mixture was concentrated under reduced (14.3 g) in ethanol was dropwise added di-tert-butyl mL), and dried over anhydrous sodium sulfate.

1.81(6H,m), 3.30-3.40(2H,m), 3.69(2H,t,J=5.4Hz), 3.66-Concentration under reduced pressure gave the title H-NMR(CDCl3): 1.26-1.39(4H,m), 1.47(9H,s), 1.61compound (24.2 g) as a colorless oil. 3.90(2H,br).

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2-(Cyclohexylamino)ethyl acetate hydrochioride Reference Example 25

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Example 24 in tetrahydrofuran were added pyridine (1.05 To a solution (50 mL) of tert-butyl cyclohexyl(2hydroxyethyl)carbamate (2.43 g) obtained in Reference

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(20 mL) was added, and the precipitated solid was collected sulfate solution (100 mL) and saturated brine (100 mL), and chloride - ethyl acetate solution (15 mL) was added. After mL), acetic anhydride (1.23 mL) and 4-dimethylaminopyridine (0.122 g) under ice-cooling, and the mixture was stirred at stirring at room temperature for 3 hrs., disopropyl ether added to the reaction mixture and the mixture was washed Ethyl acetate (100 mL) was The mixture was concentrated under reduced pressure. The residue was successively with a saturated aqueous sodium hydrogen dissolved in ethy\_ acetate (15 mL), and a 4N hydrogen carbonate solution (100 mL), a 5% aqueous copper (II) by filtration to give the title compound (1.78 g) as dried over anhydrous sodium sulfate. room temperature for 12 hrs.

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'H-NMR(DMSO-ds): 1.05-2.03(10H, m), 2.07(3H, s), 2.90-3.10(1H,m), 3.17(2H,t,J=5.2Hz), 4,29(2H,t,J=5.2Hz), 9.19(2H, br)

white solid.

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Reference Example 26

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2-(Cyclohexylamino)ethyl ethyl carbonate hydrochloride

To a solution (50 mL) of tert-butyl cyclohexyl(2-

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Example 24 in tetrahydrofuran were added pyridine (1.45 hydroxyethyl)carbamate (2.43 g) obtained in Reference and 4mL), ethyl chlorocarbonate (1.71 mL)

mixture was stirred at room temperature for 15 hrs. Ethyl acetate (100 mL) was added to the reaction mixture, and the dimethylaminopyridine (0.122 g) under ice-cooling, and the sodium hydrogen carbonate solution (100 mL), a 5% aqueous copper (II) sulfate solution (100 mL), water (100 mL) and saturated brine (100 mL), and dried over anhydrous sodium mixture was washed successively with a saturated aqueous

pressure and the residue was dissolved in ethyl acetate (15 mL). A 4N hydrogen chloride - ethyl acetate solution (15 mL) was added. After stirring at room temperature for 3 sulfate. The mixture was concentrated under reduced

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precipitated solid was collected by filtration to give the hrs., diisopropyl ether (20 mL) was added, and the title compound (2.12 g) as a white solid.

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2.90-3.10(1H,m), 3.21(2H,t,J=5.2Hz), 4.16(2H,q,J=7.0Hz),  $\text{H-NMR}(\text{DMSO-d}_{6}): \ 1.01-2.08(10\text{H,m}), \ 1.23(3\text{H,t}, J=7.0\text{Hz}),$ 

Reference Example 27

4.39(2H,t,J=5.2Hz), 9.27(2H,br).

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2-Anilinoethyl acetate hydrochloride

over anhydrous sodium sulfate, and evaporated under reduced hydrogen carbonate solution (1 L), a 5% aqueous copper (II) To a solution (700 mL) of 2-anilinoethanol (137 g) in precipitated solid was collected by filtration to give the anhydride (113.2 mL) and 4-dimethylaminopyridine (12.22 g) successively with water (1 L), a saturated aqueous sodium temperature for 20 hrs. Ethyl acetate (1 L) was added to pressure. To a solution of the obtained residue in ethyl acetate (700 mL) was added a 4N hydrogen chloride - ethyl sulfate solution (1 L) and saturated brine (1 L), dried under ice-cooling, and the mixture was stirred at room setrahydrofuran were added pyridine (97.1 mL), acetic acetate solution (250 mL) under ice-cooling, and the the reaction mixture and the mixture was washed title compound (156 g) as a white solid.

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H-NMR(CD30D): 2.11(3H,s), 3.71-3.76(2H, m), 4.32-

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4.37(2H,m), 7.49-7.64(5H,m)

Reference Example 28

tert-Butyl [2-(methylamino)-3-pyridyl]methyl carbonate

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pyridyl]methanol (2 g: synthesized according to the method To a solution (50 mL) of [2-(methylamino)-3-

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ert-butyl dicarbonate (3.48 g) and 4-dimethylaminopyridine described in WO 01/32652) in tetrahydrofuran were added di-

nl) was added to the reaction mixture and extracted with ethyl acetate (50 mL). The obtained organic layer was washed with saturated brine (50 mL), and dried over The residue obtained by (0.18 g) and the mixture was refluxed for 1 hr. anhydrous sodium sulfate. concentration under reduced pressure was purified by flash ä g acetate:hexane=1:5) to give the title compound (1.51 silica gel column chromatography (eluted with ethyl a white solid.

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'H-NMR(CDCl<sub>3</sub>): 1.49(9H,s), 3.02(3H,d,J=4.8Hz), 4.99(2H,s), 5.00(1H,bs), 6.55(1H,dd,J=7.0,5.0Hz),

7.37(1H,dd,J=7.0,1.8Hz), 8.16(1H,dd,J=5.0,1.8Hz).

Reference Example 29

15.

2-(Methylamino)benzyl acetate

To a solution (50 mL) of [2-

(methylamino)phenyl]methanol (1.37 g: synthesized according to the method described in WO 01/32652) in tetrahydrofuran and 4-dimethylaminopyridine  $(0.18~\mathrm{g})$ , and the mixture was were added pyridine (1.05 mL), acetic anhydride (1.23 mL)

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stirred at room temperature for 8 hrs. Water (100 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (100 mL). The organic layer was washed successively with a 5% aqueous copper (II) sulfate solution (50 mL), a saturated aqueous sodium hydrogen carbonate solution (50 mL) and saturated brine (50 mL)

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was evaporated under reduced pressure and the obtained residue was purified by flash silica gel column chromatography (eluted with ethyl acetate:hexane=1:5, then 1:3) to give the title compound (0.38 g) as a white solid.

14-NMR (CDCl<sub>3</sub>): 2.08(3H, s), 2.87(3H, s), 4.40(1H, br),

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mL), and dried over anhydrous sodium sulfate. The solvent

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5.08(2H,s), 6.64-6.74(2H,m), 7.17-7.32(2H,m).

Reference Example 30

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To a mixture of 2,2'-iminodiethanol (2.10 g) and ethyl acetate (20 mL) was added di-tert-butyl dicarbonate (4.37 g) under ice-cooling. After stirring for 1.5 hrs. under ice-cooling, acetic anhydride (2.08 mL), pyridine (1.78 mL) and 4-dimethylaminopyridine (0.12 g) were addec. After stirring at room temperature for 2 hrs., ethyl acetate (50 mL) was added to the reaction mixture and the mixture was

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washed with water (50 mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL). After drying over anhydrous magnesium sulfate, the mixture was

concentrated under reduced pressure. A 4N hydrogen

chloride - ethyl acetate solution (20 mL) was added to the residue, and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (10 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (6.18 g) as a white solid.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 2.07(6H,s), 3.23(4H,t,J=5.3Hz), 4.27-4.33(4H,m), 9.40(2H,br).

Reference Example 31

(S)-2-Pyrrolidinylmethyl acetate hydrochloride

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To a mixture of (S)-2-pyrrolidinylmethanol (1.01 g) and ethyl acetate (10 mL) was added di-tert-butyl dicarbonate (2.18 g) under ice-cooling. After stirring for 1 hr. under ice-cooling, acetic anhydride (1.04 mL), pyridine (0.89 mL) and 4-dimethylaminopyridine (0.061 g) were added. After stirring at room temperature for 1 hr., ethyl acetate (50 mL) was added to the reaction mixture,

and the mixture was washed with water (50 mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL).

After drying over anhydrous magnesium sulfate, the mixture was concentrated under reduced pressure. A 4N hydrogen chloride - ethyl acetate solution (10 mL) was added to the residue, and the mixture was stirred at room temperature for 1 hr. Diethyl ether (10 mL) was added and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound

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<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.56-2.10(4H,m), 2.06(3H,s), 3.05-3.24(2H,m), 3.63-3.68(1H,m), 4.15(1H,dd,J=11.8,8.1Hz), 4.26(1H,dd,J=11.8,4.1Hz), 9.21(1H,br), 9.87(1H,br).

Reference Example 32

(1.68 g) as a pale-brown solid.

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3-(Methylamino)propyl benzoate hydrochloride

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To a mixture of 3-amino-1-propanol (0.75 g) and ethyl acetate (2.25 mL) was added a solution (0.25 mL) of ditert-butyl dicarbonate (2.18 g) in ethyl acetate under icecooling. After stirring at room temperature for 21.5 hrs., benzoyl chloride (1.30 mL), pyridine (0.98 mL) and 4-dimethylaminopyridine (0.012 g) were added. After stirring

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at room temperature for 5 hrs., ethyl acetate (32.5 ml) was and washed with saturated brine (30 mL). After drying over under reduced pressure. The residue was purified by silica After After concentration under reduced pressure, ethyl acetate (10 mL) was added to filtration. After washing with diethyl ether (10 mL), the mL). The mixture was extracted with diethyl ether (80 mL) unhydrous magnesium sulfate, the mixture was concentrated into an ice-cooled aqueous ammonium chloride solution (60 gel column chromatography (ethyl acetate:hexane=2:1, then [(tert-butoxycarbonyl)(methyl)amino]propyl benzoate (2.52 the reaction mixture, and the mixture was washed ethy\_ acetate, then acetone:ethyl acetate=1:9) to give 3solid was dried under reduced pressure to give the title 60% sodium hydride (0.4 g) was irying over anhydrous magnesium sulfate, the mixture was the residue and the precipitated solid was collected by emperature for 3 hrs., the reaction mixture was poured acetate solution (10 mL) was added, and the mixture was g) as a colorless oil. A 4N hydrogen chloride - ethyl dissolved in N, N-dimethylformamide (20 mL), and methyl concentrated under reduced pressure. The residue was with water (12.5 mL) and saturated brine (12.5 mL). added under ice-cooling. After stirring at room compound (1.73 g) as a colorless solid. stirred at room temperature for 1 hr. was added. iodide (5 mL) added to

H-NMR(DMSO-ds): 2.02-2.16(2H,m), 2.56(3H,s),

3.35(2H,t,J=7.3Hz), 4.35(2H,t,J=6.1Hz), 7.51(2H,m), 7.65-

7.73(1H,m), §.01(2H,d,J=7.2Hz), 8.95(2H,br)

Reference Example 33

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2-[(Ethoxycarbonyl)(methyl)amino]ethyl ethyl carbonate

To a solution (1000 mL) of 2-(methylamino) ethanol (100 under ice-cooling. After the completion of the dropwise g) in ethyl acetate was added pyridine (222 mL), ethyl chlorocarbonate (240 mL) was dropwise added over 2 hr.

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After drying over anhydrous sodium sulfate, the mixture was temperature for 18 hrs. Water (300 mL) was added, and the compound (180 g) as a colorless fraction having a boiling concentrated under reduced pressure, and the residue was hydrochloric acid (200 mL) and saturated brine (200 mL) ethyl acetate layer was separated and washed with 1N evaporated under reduced pressure to give the title addition, the reaction mixture was stirred at room point of 95-100°C (pressure: 0.1-0.2 mmHg)

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.20-1.40(6H,m), 2.97(3H,s), 3.50-20

3.60(2H,m), 4.05-4.35(6H,m)

Reference Example 34

2-[(Chlorocarbonyl)(methyl)amino]ethyl ethyl carbonate

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To a solution (1500 mL) of 2-

refluxed for 4 days. The reaction mixture was concentrated added phosphorus oxychloride (200 mL), and the mixture was min., saturated brine (500 mL) was added, and the mixture [(ethoxycarbonyl)(methyl)amino]ethyl ethyl carbonate (150 (300 mL) by portions with stirring. After stirring for g) obtained in Reference Example 33 in acetonitrile was mixture of water (500 mL) - ice (700 g) - ethyl acetate under reduced pressure and the residue was added to

scetate layer was washed successively with saturated brine solution (300 mL) and saturated brine (300 mL), dried over pressure to give the title compound (77 g) as a colorless (300 mL), a saturated aqueous sodium hydrogen carbonate anhydrous sodium sulfate and concentrated under reduced fraction having a boiling point of  $100\text{--}105^{\circ}\text{C}$  (pressure: was extracted with ethyl acetate (500 ml). The ethyl pressure. The residue was evaporated under reduced

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'H-NMR(CDC13): 1.33(3H,t,J=7.2Hz), 3.12(3H×0.4,s), 20

0.1-0.2 mmHg).

3.22(3II×0.6, a), 3.68(2H×0.6, t, J=4.8Hz),

3.78(2H×0.4,t,J=4.8Hz), 4.23(2H,q,J=7.2Hz), 4.30-

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Reference Example 35

ter:-Butyl 4-hydroxybutylcarbamate

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acic (40 mL), water (30 mL) and saturated brine (30 mL) and the mixture was washed with water (50 mL), 1N hydrochloric under reduced pressure gave the title compound (7.54 g) as hrs., the mixture was concentrated under reduced pressure. butyl dicarbonate (8.73 g) and ethyl acetate (1 mL) under The residue was dissolved in ethyl acetate (200 mL), and ice-cooling. After stirring at room temperature for 24 acetate (9 ml,) was dropwise added a mixture of di-tert-To a mixture of 4-aminobutanol (3.57 g) and ethyl dried over anhydrous magnesium sulfate. Concentration a colorless oil.

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H-NMR(CDCl<sub>3</sub>): 1.44(9H,s), 1.47-1.61(4H,m), 3.07-3.22(2H,m), 3.61-3.76(2H,m), 4.62(1H,bs) 15

Reference Example 36

. 4-[(tert-Butoxycarbonyl)amino]butyl acetate

(3.83 g) obtained in Reference Example 35 and ethyl acetate To a mixture of tert-butyl 4-hydroxybutylcarbamate

(20 mL) were added pyridine (1.80 mL) and acetic anhydride

reaction mixture, and the mixture was washed with water (50 mL), an aqueous copper sulfate solution (30 mL), water (30 (2.27 g), and the mixture was stirred at room temperature mL) and saturated brine (30 mL) and dried over anhydrous magnesium sulfate. Concentration under reduced pressure H-NMR(CDCl<sub>3</sub>): 1.44(9H,s), 1.51-1.69(4H,m), 2.05(3H,s) for 19 hrs. Sthyl acetate (100 mL) was added to the yave the title compound (4.55 g) as a colorless oil. Ŋ

3.15(2H,m), 4.07(2H,t,J=6.5Hz), 4.55(1H,bs). Reference Example 37 10

1-(Methylamino)butyl acetate hydrochloride

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To a solution (20 mL) of 4-[(tert-

diethy] ether layer was washed with saturated brine (30 mL) mixture was extracted with diethyl ether (120 mL), and the Reference Example 36 and methyl iodide (4.85 nL) in N,Nbutoxycarbonyl)amino]butyl acetate (4.50 g) obtained in temperature for 4 hrs., the reaction mixture was poured dimethylformamide was added sodium hydride (60% in oil, into an ice - aqueous ammonium chloride solution. The 0.94 g) under ice-cooling. After stirring at room

Diethyl ether (40 mL) was added, and the precipitated and the mixture was stirred at room temperature for 2 under reduced pressure to give the title compound (2.28 g) purified by silica gel column chromatography (eluted with added a 4N hydrogen chloride - ethyl acetate solution (20 To the purified product was solid was collected by filtration. The solid was dried concentration under reduced pressure, the residue was and dried over anhydrous magnesium sulfate. After ethyl acetate:hexane=1:9). as a white solid.

"H-NMR(DMSO-d6): 1.58-1.70(4H,m), 2.01(3H,s), 2.50(3H,s), 2.82-2.90(2H,m), 4.00(2H,t,J=6.0Hz), 8.90(2H,br).

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Reference Example 38

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4-[(tert-Butoxycarbonyl)amino]butyl ethyl carbonate

(3.71 g) obtained in Reference Example 35 and ethyl acetate To a mixture of tert-butyl 4-hydroxybutylcarbamate (20 mL) were added pyridine (1.71 mL) and ethyl

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chlorocarbonate (2.55 g) under ice-cooling, and the mixture (100 mL) was added to the reaction mixture, and the mixture was stirred at room temperature for 24 hrs. Ethyl acetate was washed with water (50 mL), an aqueous copper sulfate

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solution (30 mL), water (30 mL) and saturated brine (30 mL) and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gave the title compound (4.92 g) as a colorless oil.

L.80(4H,m), 3.15(2E,m), 4.11-4.25(4H,m), 4.54(1H,bs) <sup>1</sup>H-NM3(CDCl<sub>3</sub>): 1.31(3H,t,J=7.1Hz), 1.44(9H,s), 1.46-Reference Example 39 'n

Ethyl 4-(methylamino)butyl carbonate hydrochloride

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in oil, 0.90 g) under ice-cooling. After stirring at room ml) in N,N-dimethylformamide was added sodium hydride (60% extracted with diethyl ether (120 mL). The diethyl ether obtained in Reference Example 38 and methyl iodide (4.67 layer was washed with saturated brine (30 mL) and dried temperature for 6 hrs., the reaction mixture was poured After concentration into an ice - aqueous ammonium chloride solution, and butoxycarbonyl)amino]butyl ethyl carbonate (4.90 g) To a solution (23 mL) of 4-[(tertover anhydrous magnesium sulfate.

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4N hydrogen chloride - ethyl acetate solution (20 mL), and under reduced pressure, the residue was purified by silica acetate:hexane=1:9). To the purified product was added a gel column chromatography (eluted with ethyl

the mixture was stirred at room temperature for 2 hrs. Diethyl ether (40 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.86 g) as a white solid.

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<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.21(3H,t,J=7.1Hz), 1.51-1.73(4H,m),
2.50(3H,s), 2.82-2.94(2H,m), 4.05-4.15(4H,m), 8.88(2H,br)
Reference Example 40

tert-Butyl 3-hydroxypropylcarbamate

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To a mixture of 3-aminopropanol (7.51 g) and ethyl acetate (30 mL) was dropwise added a mixture of di-tertbutyl dicarbonate (21.8 g) and ethyl acetate (3 mL) under ice-cooling. After stirring at room temperature for 22 hrs., the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL), washed with water (80 mL), 1N hydrochloric acid (60 mL), water (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the title compound (16.01 g) as a colorless oil.

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3-[(tert-Butoxycarbonyl)amino]propyl acetate

To a mixture of tert-butyl 3-hydroxypropylcarbamate (8.00 g) obtained in Reference Example 40 and ethyl acetate (50 mL) were added pyridine (4.06 mL) and acetic anhydride (5.13 g), and the mixture was stirred at room temperature for 21 hrs. Ethyl acetate (200 mL) was added to the reaction mixture, and the mixture was washed with water (100 mL), an aqueous copper sulfate solution (40 mL), water (60 mL) and saturated brine (60 mL), and dried over

(60 mL) and saturated brine (60 mL), and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the title compound (8.34 g) as a colorless oil.

<sup>1</sup>H-NVR(CDCl<sub>3</sub>): 1.44(9H,s), 1.77-1.86(2H,m), 2.06(3H,s), 3.20(2H,q,J=6.3Hz), 4.12(2H,t,J=6.3Hz), 4.67(1H,bs). Reference Example 42

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3-(Methylamino)propyl acetate hydrochloride

To a solution (80 mL) of 3-[(tert-

butoxycarbonyl)aminolpropyl acetate (17.28 g) obtained in Reference Example 41 and methyl iodide (19.8 mL) in N,N-

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3.24(2H,q,J=6.6Hz), 3.66(2H,q,J=5.1Hz), 4.73(1H,bs).

Reference Example 41

'H-NMR(CDC13): 1.45(9H,s), 1.62-1.70(2H,m),

dimethylformamide was added sodium hydride (60% in oil, 3.82 g) under ice-cooling. After stirring at room temperature for 15 hrs., the reaction mixture was poured into an ice - aqueous ammonium chioride solution and extracted with diethyl ether (300 mL). The diethyl ether layer was washed with saturated brine (100 mL), and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethy.

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acetate:hexane=1:8). To the purified product was added a 4N hydrogen chloride - ethyl acetate solution (40 mL), and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (100 mL) was added, and the precipitated solld was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.93 g) as a white solid.

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'h-NMR(DMSO-d<sub>6</sub>): 1.85-1.97(2H,m), 2.02(3H,s), 2.50(3H,s),
2.87-2.96(2H,m), 4.06(2H,t,J=6.3Hz), 8.87(2H,br).
Reference Example 43

3-[(tert-Butoxycarbonyl)amino]propyl ethyl carbonate

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H<sub>3</sub>C CH<sub>3</sub> H C CH<sub>3</sub>

To a mixture of tert-butyl 3-hydroxypropylcarbamate (8.00 g) obtained in Reference Example 40 and ethyl acetate

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(50 mL) were added pyridine (4.06 mL) and ethyl chlorocarbonate (5.95 g) under ice-cooling, and the mixture was stirred at room temperature for 24 hrs. Bthyl acetate (100 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL), an aqueous copper sulfate solution (30 mL), water (30 mL) and saturated brine (30 mL), and dried over anhydrous sodium sulfate.

Concentration under reduced pressure gave the title

compound (9.31 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.31(3H,t,J=7.1Hz), 1.44(9H,s), 1.82-1.90(2H,m), 3.22(2H,t,J=6.3Hz), 4.15-4.23(4H,m),
4.68(1H,bs).

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Reference Example 44

Ethyl 3-(methylamino)propyl carbonate hydrochloride

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To a solution (40 mL) of 3-[(tert-

butoxycarbonyl)amino]propyl ethyl carbonate (9.31 g) obtained in Reference Example 43 and methyl iodide (9.00 mL) in N,N-dimethylformamide was added sodium hydride (60% in oil, 1.82 g) under ice-cooling. After stirring at room temperature for 12 hrs., the reaction mixture was poured into an ice - aqueous ammonium chloride solution and the mixture was extracted with diethyl ether (200 mL). The

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precipitated solid was collected by filtration. The solid  $\mathrm{mL})$  , and the mixture was stirred at room temperature for 2purified by silica gel column chromatography (eluted with added a 4N hydrogen chloride - ethyl acetate solution (40 diethyl ether layer was washed with saturated brine (100ethyl acetate:hexane=1:8). To the purified product was concentration under reduced pressure, the residue was mL), and dried over anhydrous sodium sulfate. After Diethyl ether (200 mL) was added, and the

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was dried under reduced pressure to give the title compound 2.50(3H,s), 2.88-2.98(2H,m), 4.08-4.16(4H,m), 8.90(2H,br) 'H-NMR(DMSO-d<sub>6</sub>): 1.21(3H,t,J=7.1Hz), 1.91-2.00(2H,m), (4.98 g) as a white solid. Reference Example 45

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tert-Butyl (2,3-dihydroxypropyl)methylcarbamate

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of di-tert-butyl dicarbonate (51.4 g) and ethyl acetate (10 To a mixture of 3-(methylamino)-1,2-propanediol (24.5 mL) under ice-cooling. After stirring at room temperature pressure. The residue was dissolved in ethyl acetate (150  $\,$ g) and ethyl acetate (50 mL) was dropwise added a mixture for 15 hrs., the mixture was concentrated under reduced mL), and the solution was washed with water (80 mL), 1N  $\,$ 

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brine (50 mL), and dried over anhydrous sodium sulfate. hydrochloric acid (60 mL), water (50 mL) and saturated Concentration under reduced pressure gave the title compound (26.9 g) as a colorless oil.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.47(9H,s), 2.92(3H,s), 3.20-3.36(2H,m), 3.41(ZH,bs), 3.50-3.62(ZH,m), 3.73-3.88(1H,m). Reference Example 46

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3- (Methylamino) propane-1, 2-dlyl diacetate

hydrochloride

To a mixture of tert-butyl (2,3-

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pyridine (10.11 mL) and acetic anhydride (12.76 g), and the icetate (300 mL) was added to the reaction mixture, and the mixture was stirred at room temperature for 24 hrs. Ethyl mL) were added mixture was washed with water (150 mL), an aqueous copper brine (100 mL), and dried over anhydrous sodium sulfate. sulfate solution (100 mL), water (100 mL) and saturated dihydroxypropyl)methylcarbamate (10.26 g) obtained in Reference Example 45 and ethyl acetate (50

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After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with To the purified product was ethyl acetate:hexane=1:8).

was dried under reduced pressure to give the title compound The solid addec a 4N hydrogen chloride - ethyl acetate solution (40 mL), and the mixture was stirred at room temperature for precipitated solid was collected by filtration. Diethyl ether (100 mL) was added, and the (2.76 g) as a white solid.

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H-NMR(DMSO-d6): 2.03(3H,s), 2.07(3H,s), 2.55(3H,s), 3.18-3.22(2H,m), 4.09-4.28(2H,m), 5.20-5.27(1H,m), 9.01(2H,br) Reference Example 47 Diethyl 3-(methylamino)propane-1,2-diyl biscarbonate hydrochloride

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To a mixture of tert-butyl (2,3-

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mL), water (100 mL) and saturated brine (100 mL), and dried Reference Example 45 and ethyl acetate (100 mL) were added temperature for 96 hrs. Ethyl acetate (300 mL) was added to the reaction mixture, and the mixture was washed with water (150 mL), an aqueous copper sulfate solution (100 under ice-cooling, and the mixture was stirred at room dihydroxypropyl)methylcarbamate (15.53 g) obtained in pyridine (18.35 mL) and ethyl chlorocarbonate (24.62

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over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl

4N hydrogen chloride - ethyl acetate solution (80 mL), and ĝ To the purified product was added a under reduced pressure to give the title compound (5.93 The solid was dried Diethyl ether (200 mL) was added, and the precipitated the mixture was stirred at room temperature for 3 hrs. solid was collected by filtration. acetate:hexane=1:6).

3.28(2H,m), 4.10-4.43(6H,m), 5.13-5.22(1H,m), 9.14(2H,br) H-NMR(DMSO-d6): 1.20-1.28(6H,m), 2.57(3H,s), 3.12-Reference Example 48 as a white solid.

2-Ethoxyethyl 2-(methylamino)ethyl carbonate hydrochloride

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I'o a solution (20 mL) of bis(trichloromethy1) carbonate (2.97 g) in tetrahydrofuran was dropwise added a solution (2.43 mi) in tetrahydrofuran was added dropwise, and the reaction mixture was concentrated under reduced pressure under ice-cooling. Then a solution (10 mL) of pyridine mixture was stirred at room temperature for 2 hrs. The (10 mL) of 2-ethoxyethanol (1.80 g) in tetrahydrofuran

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acetate layer was washed with 0.2N hydrochloric acia (20 mL) and saturated brine (50 mL), dried over anhydrous

magnesium sulfate, and concentrated under reduced pressure

to give 2-ethoxyethyl chlorocarbonate (1.29 g). A solution (15 ni) of tert-butyl 2-hydroxyethyl (methyl) carbamate (1.23

g) obtained in Reference Example 1 in tetrahydrofuran was added pyridine (0.68 mL), and a solution (5 mL) of 2-

ethoxyethyl chlorocarbonate obtained above in

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tetrahydrofuran was dropwise added to the mixture, and the mixture was stirred at room temperature for 3 days. After

concentration of the reaction mixture under reduced pressure, water (50 mL) was added thereto and the mixture

was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with a 5% aqueous citric acid

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acetate layer was washed with a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), dried over

anhydrous magnesium sulfate. The mixture was concentrated

under reduced pressure and the residue was purified by silica gel column chromatography (eluted with ethyl

acetate:hexane=1:5, then 2:3). The purified product (1.60 g) was dissolved in diethyl ether (3 mL) and a 4N hydrogen chloride - ethyl acetate solution (3 mL) was added. The

mixture was stirred overnight at room temperature, and the 25 precipitated solid was collected by filtration and dried

under reduced pressure to give the title compound (0.94 g) as a white solid.

'H-NMR(DMSO-d6): 1.10(3H,t,J=7.0Hz), 2.57(3H,s), 3.18-

3.25(2H,m), 3.44(2H,q,J=7.0Hz), 3.56-3.60(2H,m), 4.19-

4.24(2H,m), 4.30-4.37(2H,m), 8.79(2H,br).

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Reference Example 49

3-Methoxypropyl 2-(methylamino)ethyl carbonate hydrochloride

To a mixture of lithium aluminum hydride (2.85 g) and diethyl ether (100 mL) was dropwise added slowly a solution (50 mL) of methyl 3-methoxypropanoate (11.8 g) in

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tetrahydrofuran under ice-cooling. After stirring at room temperature for 1 hr., the mixture was again ice-cooled and water (3 mL) and a 10% aqueous sodium hydroxide solution (3 mL) were dropwise added. The mixture was allowed to reach

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mu) were dropwise added. The mixture was allowed to reach room temperature, and water (9 mL) was dropwise added. The mixture was stirred for a while. The precipitate was

filtered off and the filtrate was concentrated under reduced pressure to give 3-methoxypropanol (7.64 g) as colorless oil.

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<sup>1</sup>H-NMR(CDCL<sub>3</sub>): 1.83(2H, quintet, J=5.8Hz),

2.43(1H, t, J=5.3Hz), 3.36(3H, s), 3.57(2H, t, J=6.0Hz),

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3.77 (2H, q, J=5.5Hz)

After To a solution (50 mL) of bis(trichloromethyl) carbonate ethyldiisopropylamine (5.75 mL) under ice-cooling. (4.45 g) in tetrahydrofuran was dropwise added N-

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under ice-cooling and at room temperature for 1 day. After methoxypropanol (2.70 g) obtained above in tetrahydrofuran was dropwise added. The mixture was stirred for 30 min. concentration of the reaction mixture under reduced stirring for a while, a solution (15 mL) of 3-

0.2N hydrochloric acid (30 mL) and saturated brine (30 mL), acetate (80 mL). The ethyl acetate layer was washed with pressure, diluted hydrochloric acid (50 mL) was added to dried over anhydrous magnesium sulfate and concentrated the residue, and the mixture was extracted with ethyl under reduced pressure to give 3-methoxypropyl

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of pyridine (0.65 butyl 2-hydroxyethyl (methyl) carbamate (1.75 g) obtained in chlorocarbonate (1.83 g) obtained above in tetrahydrofuran Reference Example 1 in tetrahydrofuran was added pyridine chlorocarbonate (4.39 g). To a solution (20 mL) of tertwas dropwise added, and the mixture was stirred at room tetrahydrofuran was added and the mixture was further (0.97 ml) and a solution (5 ml) of a 3-methoxypropyl mL) and 3-methoxypropyl chlorocarbonate (1.22 g) in A solution (5 mL) temperature for 2 hrs.

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under reduced pressure and water (50 mL) was added to the

residue. The mixture was extracted with ethyl acetate (80 purified by silica gel column chromatography (eluted with agueous citric acid solution (50 mL) and saturated brine NL), and the ethyl acetate layer was washed with a 5% concentrated under reduced pressure. The residue was (50 mL), dried over anhydrous magnesium sulfate and

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cemperature and the reaction mixture was concentrated under ethyl acetate:hexane=1:9, then 3:7). The purified product Ø 3.40 g) was dissolved in diethyl ether (5 mL) and a 4N as hydrogen chloride - ethyl acetate solution (5 mL) was erystallization to give the title compound (2.06 g) The mixture was stirred overnight at room reduced pressure. Diethyl ether was added for added.

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H-NMR(DMSO-d6): 1.78-1.90(2H,m), 2.54(3H,s), 3.15-3.25(2H,m), 3.23(3H,s), 3.33-3.42(2H,m) colorless solid.

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1.16(2H,t,J=6.0Ez), 4.36(2H,t,J=6.0Hz), 9.27(2H,br) Reference Example 50

2-(Methylamino)ethyl N,N-dimethylglycinate

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dihydrochloride

A mixture of tert-butyl 2-

The reaction mixture was concentrated

stirred for 1 hr.

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S S S To a solution (50 mL) of tert-butyl 2-hydroxyethyl(methyl)carbamate (3.50 g) obtained in Reference Example 1, thioacetic acid (1.72 mL) and

triphenylphosphine (7.87 g) in tetrahydrofuran was dropwise added slowly a solution (10 mL) of diisopropyl azodicarboxylate (5.91 mL) in tetrahydrofuran under icecoling. The mixture was stirred under ice-cooling for 1 hr. and at room temperature for 2 hrs. The reaction

mixture was again ice-cooled and a solution (10 mL) of triphenylphosphine (7.87 g) and diisopropyl azodicarboxylate (5.91 mL) in tetrzhydrofuran was added. The mixture was stirred under ice-cooling for 30 min. Thioacetic acid (1.14 mL) was added and the mixture was

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stirred under ice-cooling for 30 min. and at room temperature overnight. The reaction mixture was concentrated under reduced pressure and hexane and disopropyl ether were added to the residue. The precipitate was filtered off and the filtrate was

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concentrated under reduced pressure. This step was repeated and a saturated aqueous sodium hydrogen carbonate solution (50 mL) was added. The mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed

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then 20:80). IN Hydrochloric acid (24 mL) was added to the and a saturated aqueous sodium hydrogen carbonate solution anhydrous magnesium sulfate and concentrated under reduced extracted with ethyl acetate (100 mL). The ethyl acetate (5.29 g), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide layer was washed with saturated brine (50 mL), dried over reaction mixture was concentrated under reduced pressure dimethylaminopyridine (1.22 g) and N,N-dimethylformamide pressure. The residue was purified by silica gel column overnight at room temperature. The reaction mixture was chromatography (eluted with methanol:ethyl acetate=5:95, mL) was stirred overnight at room temperature. The purified product (2.46 g), and the mixture was stirred Reference Example 1, N, N-dimethylglycine hydrochloride nydroxyethyl (methyl) carbamate (3.50 g) obtained in (50 mL) was added to the residue. The mixture was hydrochloride (7.67 g), triethylamine (5.58 mL),

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'H-NMR(DMSO-d6): 2.52(3H,s), 2.85(6H,s), 3.20(2H,m), 4.30(2H,s), 4.43-4.49(2H,m), 9.60(2H,br), 10.81(1H,br) Reference Example 51

concentrated under reduced pressure to give the title

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compound (2.14 g) as a colorless solid.

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S-[2-(Methylamino)ethyl] thioacetate hydrochloride

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magnesium sulfate and concentrated under reduced pressure. with saturated brine (50 mL), dried over anhydrous The residue was purified by silica gel column

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solution (10 mL) was added to the purified product (4.47 g) chromatography (eluted with ethyl acetate:hexane=5:95, and pressure and ethyl acetate and diethyl ether were added to the residue for crystallization to give the title compound and the mixture was stirred overnight at room temperature. then 15:85). A 4N hydrogen chloride - ethyl acetate The reaction mixture was concentrated under reduced (1.79 g) as a pale-yellow solid.

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'H-NMR(DMSO-d<sub>6</sub>): 2.38(3H,s), 2.52(3H,s), 2.96-3.C8(2H,m), 3.12-3.20(2H,m), 9.35(2H,br).

Reference Example 52

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Ethyl 2-[2-(methylamino)ethoxy]ethyl carbonate hydrochloride

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To a mixture of 2-(2-aminoethoxy) ethanol (99.52 g) and tert-butyl dicarbonate (208.57 g) and ethyl acetate (50 mL) under ice-cooling. After stirring at room temperature for pressure. The residue was dissolved in ethyl acetate (500 ethyl acetate (200 mL) was dropwise added a mixture of di-60 hrs., the mixture was concentrated under reduced

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and saturated brine (300 mL), and dried Concentration under reduced mL), washed with water (200 mL), 1N hydrochloric acid (200 over anhydrous sodium sulfate. pressure gave tert-butyl [2-(2mL), water (300 mL)

hydroxyethoxy)ethyl]carbamate (169.2 g) as a colorless oil H-NMR(CDCL<sub>3</sub>): 1.45(9H,s), 3.33(2H,q,J=5.1Hz), 3.54-

3.59(4H,m), 3.74(2H,q,J=5.1Hz), 4.88(2H,bs).

To a mixture of tert-butyl [2-(2-

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acetate (500 mL) was added to the reaction mixture, and the nydroxyethoxy)ethyl]carbamate (53.93.g) obtained above and ethyl chlorocarbonate (70.57 g) under ice-cooling, and the Ethy] ethyl acetate (350 mL) were added pyridine (53.78 mL) and mixture was washed with water (500 mL), an aqueous copper mixture was stirred at room temperature for 96 hrs.

æ butoxycarbonyl)amino]ethoxy]ethyl ethyl carbonate (93.19 sulfate solution (200 mL), water (300 mL) and saturated orine (300 mL) and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave 2-[2-[(tertas a colorless oil.

J=5.1Hz), 3.54(2H,t, J=5.1Hz), 3.67-3.74(2H,m), 4.21(2H,q, 'H-NMR(CDC13): 1.32(3H,t,J=7.2Hz), 1.44(9H,s), 3.32(23,t, J=7.2Hz), 4.26-4.31(2H,m), 4.91(1H,bs). 20

To a solution (350 mL) of 2-[2-[(tert-

g butoxycarbonyl)amino]ethoxy]ethyl ethyl carbonate (93.15 obtained above and methyl iodide (83.6 mL) in N,N-

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temperature for 24 hrs., the reaction mixture was poured dimethylformamide was added sodium hydride (60% in oil, into an ice - aqueous ammonium chloride solution, and 16.12 g) under ice-cooling. After stirring at room

under reduced pressure, the residue was purified by silica layer was washed with saturated brine (300 mL), and dried extracted with diethyl ether (800 mL). The diethyl ether over anhydrous magnesium sulfate. After concentration gel column chromatography (eluted with ethyl

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was dried under reduced pressure to give the title compound precipitated solid was collected by filtration. The solid 4N hydrogen chloride - ethyl acetate solution (300 mL) was added, and the mixture was stirred at room temperature for acetate:hexane=1:8). To the purified product was added a 2 hrs. Diethyl ether (300 mL) was added, and the (33.21 g) as a white solid. 15

'H-NMR(DMSO-dε): 1.21(3H,t,J=7.2Hz), 2.51(3H,s), 3.02-

3.09(2H,m), 3.65-3.72(4H,n), 4.12(2H,q,J=7.2Hz)

4.22(23,t,J=4.5Hz), 9.06(2H,br).

Reference Example 53

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Ethyl 2-[methyl[[2-

(methylamino)ethoxy]carbonyl]amino]ethyl carbonate hydrochloride

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To a solution (100 mL) of

bis(trichloromethy1) carbonate (11.87 g) in tetrahydrofuran

ethyl acetate and triethylamine (10.0 mL) under ice-cooling After stirring under washed with water (150 mL) and saturated brine (200 mL) and was dropwise added a solution (20 mL) of pyridine (9.71 mL) and the mixture was stirred at room temperature for 15 hrs. the mixture was stirred at room temperature for 15 hrs. mixture was stirred at room temperature for 48 hrs. Ethyl After concentration under reduced pressure, water (500 mL) ice-cooling for 30 min., a solution (20 mL) of tert-butyl Reference Example 1 in tetrahydrofuran was dropwise added dried over anhydrous sodium sulfate. After concentration ethyl chlorocarbonate (3.44 g) under ice-cooling, and the Sthyl acctate (300 mL) was added to the reaction mixture, othyl acetate (100 mL) were added pyridine (2.91 mL) and under reduced pressure, to a mixture of the residue and To the obtained residue were added a and anhydrous sodium sulfate were added to the residue. 'n :-hydroxyethyl(methyl)carbamate (17.52 g) obtained in After filtration, the filtrate was concentrated under solution (50 mL) of 2-(methylamino)ethanol (5.00 g) in tetrahydrofuran under ice-cooling. reduced pressure. S 10 15 20

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acetate (200 mL) was added to the reaction mixture, washed with water (100 mL), an aqueous copper sulfate solution (50 mL), water (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate. The mixture was

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concentrated under reduced pressure and the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:3). To the purified product was added a 4N hydrogen chloride - ethyl acetate solution (30 mL), and the mixture was stirred at room temperature for 3 hrs. Diethyl ether (100 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.90 g) as a white solid.

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<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): 1.21(3H,t,J=7.2Hz), 2.57(3H,bs),

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2.86(1.5H,s), 2.93(1.5H,s), 3.16(2H,bs), 3.34(1H,bs), 3.48(1H,t,J=5.1Hz), 3.58(1H,t,J=5.1Hz), 4.12(2H,q,J=7.2Hz),

Reference Example 54

4.16-4.24(4H,m), 8.94(1H,br)

2-(Methylamino)ethyl 1-methylpiperidine-4-carboxylate
dihydrochloride

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A mixture of ethyl piperidine-4-carboxylate (4.72 g),

methyl iodide (2.24 mL), potassium carbonate (8.29 g) and acetonitrile (50 mL) was stirred at room temperature for 2 hrs. The reaction mixture was concentrated under reduced pressure and water (150 mL) was added. The mixture was

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extracted with ethyl acetate (150 mL). The ethyl acetate layer was washed with saturated brine (100 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. A 1N aqueous sodium hydroxide solution (20 mL) was added to the residue (2.64 g), and the mixture was stirred overnight at room temperature. The reaction mixture was neutralized by adding 1N hydrochloric acid (20 mL) and the mixture was concentrated under reduced pressure. Ethanol was added to the residue, and the precipitate was filtered off. The filtrate was

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concentrated under reduced pressure. This step was repeated and ethanol and ethyl acetate were added to the residue for crystallization to give 1-methylpiperidine-4-carboxylic acid (1.79 g) as a colorless solid.

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'H-NMR(CD3OD): 1.80-1.98(2H,m), 2.00-2.14(2H,m), 2.28-

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2.42(1H,m), 2.78(3H,s), 2.88-3.04(2H.m), 3.32-3.44(2H.m).
A mixture of 1-methylpiperidine-4-carboxylic acid (1.72 g)
obtained above, text-butyl 2-hydroxyethyl(methyl)carbamate
(1.75 g) obtained in Reference Example 1, 1-ethyl-3-[3-(dimethylemino)propyl]carbodiimide hydrochloride (2.30 g),

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4-dimethylaminopyridine (0.24 g) and acetonitrile (50

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then 80:20). 1N Hydrochloric acid (25 mL) was added to the magnesium sulfate and concentrated under reduced pressure. washed with saturated brine (50 mL), dried over anhydrous was stirred at room temperature for 16 hrs. The reaction with ethyl acetate (100 mL). The ethyl acetate layer was The mixture was extracted saturated aqueous sodium hydrogen carbonate solution (50 overnight at room temperature. The reaction mixture was acded. The mixture was again concentrated under reduced concentrated under reduced pressure and isopropanol was chromatography (eluted with ethyl acetate:hexane=50:50, purified product (2.73 g), and the mixture was stirred mixture was concentrated under reduced pressure and a pressure and the precipitated solid was collected by The residue was purified by basic silica gel column Ø filtration to give the title compound (1.72 g) as mL) was added to the residue. colorless solid.

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'H-NMR(DMSO-d<sub>6</sub>): 1.70-2.20(4H,m), 2.40-3.50(13H,m), 4.31(2H,m), 9.25(2H,br), 10.77(1H,br).

Reference Example 55 2-[[4-(Aminocarbonyl)phenyl]amino]ethyl acetate

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A mixture of 4-fluorobenzonitrile (6.06 g), 2-

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aminoethanol (3.71 g), potassium carbonate (8.29 g) and cimethyl sulfoxide (50 mL) was stirred at 100°C overnight. Water (200 mL) was added to the reaction mixture and the

mixture was extracted with ethyl acetate (200 mL\*4). The ethyl acetate layer was washed with saturated brine (100 mL), dried over anhydrous magnesium sulfate and

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concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=30:70, then 50:50, then 80:20, then

hydroxyethyl)aminolbenzonicrile (5.89 g) as a yellow solid.

<sup>1</sup>H-NWR(CDCL<sub>3</sub>): 2.04(1H,t,J=4.8Hz), 3.33(2H,m),

ethyl acetate) to give 4-[(2-

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3.86(2H, q, J=4.8Hz), 4.66(1H, br), 6.58(2H, d, J=8.7Hz),

7.39(2H, d, J=8.7Hz).

A mixture of 4-[(2-hydroxyethyl)amino]benzonitrile (0.81 g) obtained above, potassium hydroxide (1.12 g) and tertbutanol (20 mL) was stirred at 100°C for 1 hr. Water (100 mL) was added to the reaction mixture, and extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed

with saturated brine (80 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure.

To a solution (10 mL) of the residue (0.83 g), pyridine (0.49 mL) and 4-dimethylaminopyridine (0.061 g) in tetrahydrofuran was dropwise added a solution (1 mL) of acetic anhydride (0.57 mL) in tetrahydrofuran. The mixture

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was added, and the mixture was extracted with ethyl acetate residue was purified by silica gel column chromatography was stirred at room temperature for 1 hr., water (80 ml) saturated brine (80 mL), dried over anhydrous magnesium (eluted with ethy\_ acetate:hexane=30:70, then 60:40) to sulfate and concentrated under reduced pressure. The give the title compound (0.68 g) as a colorless solid. mL). The ethyl acetate layer was washed with 'H-NMR(CDCl<sub>3</sub>): 2.08(3H,s), 3.44(2H,q,J=5.6Hz),

4.29(2H,t,J=5.4Hz), 4.48(1H,br), 6.59(2H,d,J=8.9Hz), 7.43(2H, d, J=8.9Hz).

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Reference Example 56

2-(Methylamino)ethyl 1-methyl-4-piperidinyl carbonate dihydrochloride

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(3.36 g) in tetrahydrofuran was dropwise added slowly a To a solution (40 mL) of N, N'-carbonyldiimidazole solution (10 mL) of tert-butyl 2-

The mixture was stirred under ice-cooling for 40 min. and Reference Example 1 in tetrahydrofuran under ice-cooling. at room temperature for 2 hrs. N,N'-Carbonyldiimidazole hydroxyethyl (methyl) carbamate (3.30 g) obtained in

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(0.31 g) was added and the mixture was further stirred for the residue. The mixture was washed with saturated brine reduced pressure and ethyl acetate (150 mL) was added to (100 mL×2), water (50 mL×3) and saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated The reaction mixture was concentrated under butoxycarbonyl) (methyl) amino]ethyl lH-imidazole-1under reduced pressure to give 2-[(tertcarboxylate (5.24 g) as a colorless oil.

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H-NMR(CDCl<sub>3</sub>): 1.39(9H×0.5,s), 1.42(9H×0.5,s), 2.94(3H,m), 3.63(2H,m), 4.51(2H,t,J=5.3Hz), 7.06(1H,m), 7.42(1H,m), 8.13(1H,s). 10

A mixture of 2-[(tert-

outoxycarbonyl) (methyl) amino]ethyl 1H-imidazole-1-

carboxylate (1.35 g) obtained above, 1-methyl-4-piperidinol added and the mixture was stirred overnight. The reaction (1.38 g) and acetonitrile (20 mL) was stirred overnight at saturated aqueous sodium hydrogen carbonate solution (50 coom temperature. 1-Methyl-4-piperidinol (0.92 g) was mixture was concentrated under reduced pressure and 15 20

1N Hydrochloric acid (12 mL) was added to the residue (1.60 magnesium sulfate and concentrated under reduced pressure.

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washed with saturated brine (50 mL), dried over anhydrous

with ethyl acetate (100 mL). The ethyl acetate layer was

nL) was added to the residue. The mixture was extracted

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reduced pressure, water, isopropanol and ethyl acetate were temperature. The reaction mixture was concentrated under added, and the precipitated solid was collected by filtration to give the title compound (1.09 g) as g), and the mixture was stirred overnight at room

'H-NMR(DMSO-d<sub>6</sub>): 1.85-2.20(4H,m), 2.55(3H,s),

colorless solid.

2.70(33×0.5,s), 2.73(3H×0.5,s), 2.90-3.50(6H,m),

4.38(2H,m), 4.65-5.00(1H,m), 9.21(2H,br), 11.10(1H,br)

Synthetic Example 1

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trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-lHbenzimidazo\_-1-yl]carbonyl]amino]ethyl acetate 2-[Methy1[[(R)-2-[[[3-methy1-4-(2,2,2-

To a solution (30 mL) of bis(trichloromethyl) carbonate (methylamino)ethyl acetate hydrochloride (0.77 g) obtained mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-4 (0.50 g) in tetrahydrofuran was dropwise added a solution After stirring under ice-cooling for 30 min., cooling.

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added and the mixture was stirred at room temperature for 1 After concentration under reduced pressure, water (50 anhydrous magnesium sulfate. The mixture was concentrated with ethyl acetate (50 mL). The ethyl acetate layer was was added to the residue. The mixture was extracted in Reference Example 2 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise washed with saturated brine (50 mL) and dried over

inder reduced pressure, and the residue was dissolved in dimethylaminopyridine (catalytic amount) were added, and 4tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2penzimidazole (1.11 g), triethylamine (0.84 mL) and the mixture was stirred at 60°C overnight. After trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-1H-

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added to the residue. The mixture was extracted with ethyl saturated brine (50 mL) and dried over anhydrous magnesium acetate (50 ml). The ethyl acetate layer was washed with concentration under reduced pressure, water (50 mL) was sulfate. After concentration under reduced pressure,

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ethyi acetate, then acetone:ethyl acetate=1:4, then 1:1) to chromatography (eluted with ethyl acetate:hexane=1:1, then chromatography (eluted with ethyl acetate:hexane=2:1, then give the title compound (1.13 g) as a yellow amorphous sthyl acetate), and further by silica gel column residue was purified by basic silica gel column

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solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.10(3H,s), 2.24(3H,s), 3.09(3H,bs), 3.60-4.00(2H,br), 4.25-4.50(4H,m), 4.89(1H,d,J=13.3Hz),

5.05(1H, d, J=13.3Hz), 6.65(1H, d, J=5.5Hz), 7.35-7.51(3H, m),

7.80-7.90(1H,m), 8.35(1H,d,J=5.5Hz).

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Synthetic Example 2

2-[Methy1[[(R)-2-[[(3-methy1-4-(2,2,2trifluoroethoxy)-2-pyridy-]methy1]sulfiny1]-lifbenzimidazol-1-y1]carbony1]amino]ethy1 trimethylacetate

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To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (3.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., 2-(methylamino)ethyl trimethylacetate hydrochloride (0.98 g) obtained in Reference Example 3 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred overnight at

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room temperature. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL), and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methy]-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-IH-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037

triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred overnight at 60°C. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate 13 layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration

layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:3, then 3:2). Crystallization from acetone-diisopropyl ether and recrystallization from

g)as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.23(9H,s), 2.23(3H,s), 3.08(3H,bs), 3.40-4.30(2H,br), 4.30-4.50(4H,m), 4.80-5.20(2H,br),

acetone-diisopropyl ether gave the title compound (1.01

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25 6.64(1H,d,J=5.7Hz), 7.35-7.50(3H,m), 7.78-7.88(1H,m),

8.35(1H, d, J=5.7Hz). Synthetic Example 3 2-[Methy1[[(R)-2-[[[3-methy1-4-(2,2,2trifluoroethoxy)-2-pyridyl]methy1]sulfinyl]-1Hbenzimidazol-1-yl]carbonyl]amino]ethyl
cyclohexanecarboxylate

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To a solution (30 mL) of bis(trichloromethyl) carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl cyclohexane. carboxylate hydrochloride (1.11 g) obtained in Reference Example 4 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 1 hr. After concentration

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ML). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-

5 [[[3-Methyl-4-(2,2,2-trifiluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lH-benzimidazole (1.11 g),
triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037
g) were added, and the mixture was stirred overnight at
60°C. After concentration under reduced pressure, water

(50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash

silica gel column chromatography (eluted with acetone:hexane=1:3, then 3:2). Crystallization from acetone-diisopropyl ether and recrystallization from acetone-diisopropyl ether gave the title compound (1.11 g) as a colorless solid.

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20 <sup>1</sup>H-NMR(CDCL<sub>3</sub>): 1.10-1.55(5H,m), 1.55-1.82(3H,m), 1.84-1.98(2H,m), 2.23(3H,s), 2.27-2.40(1H,m), 3.08(3H,bs), 3.40-4.30(2H,br), 4.30-4.50(4H,m), 4.80-5.15(2H,br), 6.64(1H,d,J=5.4Hz), 7.35-7.48(3H,m), 7.84(1H,d,J=6.9Hz), 8.34(1H,d,J=5.4Hz).

25 Synthetic Example 4

residue. The mixture was extracted with ethyl acetate (50

under reduced pressure, water (50 mL) was added to the

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lHbenzimidazol-1-yl]carbonyl]amino]ethyl benzoate

To a solution (30 mL) of bis(trichloromethyl) carbonate (methylamino)ethyl benzoate hydrochloride (1.08 g) obtained (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-(0.50 g) in tetrahydrofuran was dropwise added a solution cooling. After stirring under ice-cooling for 1 hr., 2temperature. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate concentrated under reduced pressure, and the résidue was οť layer was washed with saturated brine (50 mL) and dried triethylamine (0.70 mL) in tetrahydrofuran was dropwise A solution (1 mL) added, and the mixture was stirred overnight at room over anhydrous magnesium sulfate. The layer was in Reference Example 5 was added.

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dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinylj-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred overnight at 60°C. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After

concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:3, then 3:2). Crystallization from acetone-diethyl ether and recrystallization from acetonediethyl ether gave the title compound (1.09 g) as a

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"H-NMR(CDCl<sub>3</sub>): 2.22(3H,s), 3.12(3H,bs), 3.50-4.30(2H,br), 4.37(2H,q,J=7.8Hz), 4.68(2H,m), 4.80-5.20(2H,br), 6.63(1H,d,J=5.7Hz), 7.26-7.48(5H,m), 7.53-7.61(1H,m), 7.82(1H,d,J=8.1Hz), 8.04(2H,d,J=7.2Hz), 8.33(1H,d,J=5.7Hz)

colorless solid.

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2-[Methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl benzoate

Synthetic Example 5

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To a solution (30 mL) of bis(trichloromethyl) carbonate (methylamino)ethyl benzoate hydrochloride (2.16 g) obtained cooling. After stirring under ice-cooling for 30 min., 2saturated brine (50 mL) and dried over anhydrous magnesium (2 mL) of pyridine (0.81 nL) in tetrahydrofuran under iceresidue was dissolved in tetrahydrofuran (40 mL). 2-[[[3-(0.99 g) in tetrahydrofuran was dropwise added a solution sulfate. After concentration under reduced pressure, the ethyl acetate layer was separated and taken, washed with temperature for 1 hr. After concentration under reduced pressure, ethyl acetate (100 mL) and water (100 mL) were in Reference Example 5 was added. After addition of a added to the residue, and the mixture was stirred. tetrahydrofuran, the mixture was stirred at room solution (2 mL) of triethylamine (1.39 mL) in Methyl-4-(2,2,2-trifluoroethoxy)-2-

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pyridyl]methyl]sulfinyl]-1H-benzimidazole (2.90 g),

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triethylamine (2.20 mL) and 4-dimethylaminopyridine (0.096 g) were added, and the mixture was stirred at 60°C for 2 hr. After concentration under reduced pressure, ethyl acetate (150 mL) and water (80 mL) were added to the

- residue, and the mixture was stirred. The ethyl acetate layer was separated and taker, washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with
  - ethyl acetate:hexane=1:1, then ethyl acetate).
    Recrystallization from acetone gave the title compound (2.62 g) as a colorless solid.

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.22(3H,s), 3.13(3H,bs), 3.68-3.98(2H,bm), 4.38(2H,q,J=7.8Hz), 4.69(2H,m), 4.80-5.10(2H,bm), 6.64(1H,d,J=5.7Hz), 7.27-7.48(5H,m), 7.59(1H,m), 7.83(1H,m), 8.06(2H,d,J=6.0Hz), 8.35(1H,d,J=5.7Hz).

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2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

Synthetic Example 6

20 benzimidazol-1-yl]carbonyl]amino]ethyl 4-methoxybenzoate

To a solution (18 mL) of bis(trichloromethyl) carbonate mL) of triethylamine (0.84 mL) in tetrahydrofuran was added (80 mL) and water (50 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated methylamino)ethyl 4-methoxybenzoate hydrochloride (1.48 g) and the mixture was stirred at room temperature for 80 min. (0.584 g) in tetrahydrofuran was dropwise added a solution cooling. After stirring under ice-cooling for 40 min., 2-(1 mL) of pyridine (0.49 mL) in tetrahydrofuran under iceobtained in Reference Example 6 was added. A solution (1 After concentration under reduced pressure, ethyl acetate and dried over anhydrous magnesium sulfate. After concentration tetrahydrofuran (25 mL). (R)-2-[[[3-Methy1-4-(2,2,2under reduced pressure, the residue was dissolved in trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hand taken, washed with saturated brine (30 mL)

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dimethylaminopyridine (0.051 g) were added, and the mixture chromatography (eluted with ethyl acetate:hexane=1:1, then reduced pressure, ethyl acetate (150 mL) and water (50 mL) was stirred at 60°C for 3 hrs. After concentration under the ethyl acetate layer was separated and taken, washed pressure, the residue was purified by silica gel column were added to the residue, and the mixture was stirred. nexane gave the title compound (1.08 g) as a colorless benzimidazole (1.55 g), triethylamine (1.17 mL) and 4ethyl acetate). Recrystallization from ethyl acetatewith saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced solid. 10

5.14(2H,bm), 6.63(1H,d,J=5.7Hz), 6.91(2H,d,J=9.0Hz), 7.27-H-NMR(CDC13): 2.22(3H,s), 3.11(3H,bs), 3.68-3.90(2H,bm), 3.85(3H,s), 4.37(2H,q,J=7.9Hz), 4.58-4.72(2H,m), 4.82-7.40(3H,m), 7.82(1H,m), 7.99(2H,d,J=9.0Hz), 15

Synthetic Example 7 3.33 (1H, d, J=5.7Hz).

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benzimidazol-1-yljcarbonyl]amino]ethyl 3-chlorobenzoate trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-2-[Methy1[[(R)-2-[[[3-methy1-4-(2,2,2-

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H<sub>3</sub>C<sub>1</sub>N<sub>1</sub>C<sub>1</sub>N<sub>2</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3</sub>C<sub>1</sub>N<sub>3<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To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under icecooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 3-chlorobenzoate hydrochloride (1.50 g) obtained in Reference Example 7 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (40 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (25 mL) and dried over anhydrous magnesium sulfate. The layer was

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concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.44 g), triethylamine (1.09 mL) and 4-

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dimethylaminopyridine (0.048 g) were added, and the mixture was stirred at 60°C for 3 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (40 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column

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chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (0.84 g) as colorless syrup.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.21(3H, s), 3.12(3H, bs), 3.78-4.08(2H, bm), 4.38(2H, g, J=7.8Hz), 4.64-5.08(4H, bm), 6.64(1H, d, J=5.2Hz), 7.34-7.42(4H, m), 7.56(1H, m), 7.82(1H, m),

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7.94(1H,d,J=7.6Hz), 8.02(1H,s), 8.34(1H,d,J=5.2Hz). Synthetic Example 8

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2-[Methyll[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridy.]methyl]sulfinyl]-1Hbenzimidazo.-1-yl]carbony.]amino]ethyl 3,4-difluorobenzoate

To a solution (20 mL) of bis(trichloromethyl) carbonate (R)-2-[[[3-Methyl-4-(methylamino)ethyl 3,4-difluorobenzoate hydrochloride (1.51 acetate (80 mL) and water (50 mL) were added to the residue (0.582 g) in tetrahydrofuran was dropwise added a solution cooling. After stirring under ice-cooling for 30 min., 2and dried over anhydrous magnesium sulfate. The layer was (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under iceadded and the mixture was stirred at room temperature for g) obtained in Reference Example  $\theta$  was added. A solution The ethyl acetate layer was (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was concentrated under reduced pressure, and the residue was separated and taken, washed with saturated brine (30 mL)  $\,$ hrs. After concentration under reduced pressure, ethyl (2, 2, 2-trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-1Hdissolved in tetrahydrofuran (25 mL). and the mixture was stirred.

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benzimidazole (1.71 g), triethylamine (1.29 mL) and 4dimethylaminopyridine (0.056 g) were added, and the mixture
was stirred at 60°C for 17 hrs. After concentration under
reduced pressure, ethyl acetate (100 mL) and water (50 mL)
were added to the residue, and the mixture was stirred.

The ethyl acetate layer was separated and taken, and the
aqueous layer was extracted with ethyl acetate (20 mL).

Ethyl acetate layers were combined, washed with saturatec
brine (30 mL) and dried over anhydrous magnesium sulfate.

After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then 2:1), and by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1). Crystallization from acetone-

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diisopropyl ether and recrystallization from ethyl acetatehexane gave the title compound (1.37 g) as a colorless solid.

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'H-NMR(CDCl<sub>3</sub>): 2.21(3H,s), 3.11(3H,bs), 3.82-4.08(2H,bm), 4.38(2H,q,J=7.8Hz), 4.60-5.14(4H,bm), 6.63(1H,d,J=5.7Hz),

20 7.20(1H,m), 7.33-7.41(3H,m), 7.78-7.92(3H,m), 8.33(1H,d,J=5.7Hz).

Synthetic Example 9

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

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trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

benzimidazol-1-yl]carbonyl]amino]ethyl

rifluoromethoxybenzoate

To a solution (20 mL) of bis(trichloromethyl) carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 4-trifluoromethoxybenzoate hydrochloride (1.79 g) obtained in Reference Example 9 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 1.5 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (50 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the

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triethylamine (1.18 mL) and 4-dimethylaminopyridine (0.052 g) were added, and the mixture was stirred at  $60^{\circ}\text{C}$  for 4.5ethyl acetate:hexane=1:1), and further by basic silica gel purified by silica gel column chromatography (eluted with layers were combined, washed with saturated brine (30 mL) residue was dissolved in tetrahydrofuran (25 mL). (R)-2residue, and the mixture was stirred. The ethyl acetate extracted with ethyl acetate (30 mL). The ethyl acetate layer was separated and taken, and the aqueous layer was hrs. After concentration under reduced pressure, ethyl concentration under reduced pressure, the residue was acetate (100 mL) and water (50 mL) were added to the pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.57 g), and dried over anhydrous magnesium sulfate. After [[[3-Methy1-4-(2,2,2-trifluoroethoxy)-2-10 15

colorless syrup.

<sup>1</sup>H-NNR(CDCl<sub>3</sub>): 2.22(3H,s), 3.11(3H,bs), 3.85-4.05(2H,bm),

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<sup>4</sup>.38(2H,q,J=7.8Hz), 4.60-5.12(4H,bm), 6.64(1H,d,J=5.7Hz),

7.24(2H,d,J=8.7Hz), 7.25-7.40(3H,m), 7.82(1H,d,J=7.2Hz),

8.09(2H,d,J=8.7Hz), 8.33(1H,d,J=5.7Hz).

Synthetic Example 10

acetate:hexane=1:1) to give the title compound (1.44 g) as

column chromatography (eluted with ethyl

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

25 trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

benzimidazol-1-yl]carbonyl]amino]ethyl 4-fluorobenzoate

To a solution (20 mL) of bis(trichloromethyl) carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under icecooling. After stirring under ice-cooling for 30 min., 2-(methylamino) ethyl 4-fluorobenzoate hydrochloride (1.40 g) obtained in Reference Example 10 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (40 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-

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(2,2,2-triflucroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazole (1.32 g), triethylamine (1.00 mL) and 4dimethylaminopyridine (0.049 g) were added, and the mixture
was stirred at 60°C for 14.5 hrs. After concentration

5 under reduced pressure, ethyl acetate (150 mL) and water
(50 mL) were added to the residue, and the mixture was
stirred. The ethyl acetate layer was separated and taken,
washed with saturated brine (30 mL) and dried over
anhydrous magnesium sulfate. After concentration under
10 reduced pressure, the residue was crystallized from ethyl

reduced pressure, the residue was crystallized from ethyl acetate:hexane=1:1 and collected by filtration.

Recrystallization from acetone gave the title compound (1.39 g) as a colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.22(3H,s), 3.12(3H,bs), 3.78-4.20(2H,bm),
4.38(2H,q,J=7.8Hz), 4.58-5.08(4H,bm), 6.65(1H,d,J=5.6Hz),
7.11(2H,t,J=8.4Hz), 7.28-7.44(3H,m), 7.81-7.86(1H,m), 8.03-8.11(2H,m), 8.35(1H,d,J=5.6Hz).

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Synthetic Example 11

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lHbenzimidazol-1-yl]carbonyl]amino]ethyl 3,4,5trimethoxybenzoate

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To a solution (30 mL) of bis(trichloromethyl) carbonate (0.60g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., 2-(methylamino)ethyl 3,4,5-teimethoxybenzoate hydrochloride (1.22 g) obtained in Reference Example 11 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with dilute hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was

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dimethylaminopyridine (0.037 g) were added, and the mixture dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-2 days. After concentration under reduced pressure, water was stirred at 60°C for 3 hrs. and at room temperature for under reduced pressure, the residue was purified by flash extracted with ethyl acetate (50 mL). The ethyl acetate scetone:hexane=1:3, then 3:2) to give the title compound layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration (2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazole (1.11 g), triethylamine (0.84 mL) and The mixture was silica gel column chromatography (eluted with (1.56 g) as a yellow amorphous solid. (50 mL) was added to the residue. S 10

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.21(3H,s), 3.12(3H,bs), 3.50-4.30(2H,br), 3.83(6H,s), 3.90(3H,s), 4.38(2H,q,c=7.8Hz), 4.67(2H,m), 4.80-5.15(2H,br), 6.64(1H,d,J=5.7Hz), 7.25-7.40(5H,m), 7.78-7.86(1H,m), 8.33(1H,d,J=5.7Hz).

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2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazol-1-yl]carbonyl]amino]ethyl 2pyridinecarboxylate

Synthetic Example 12

To a solution (30 mL) of bis(trichloromethyl)carbonate Reference Example 12 was added. After dropwise addition of The precipitated solid was filtered pressure. The residue was dissolved in tetrahydrofuran (10 triethylamine (0.99 mL) and 4-dimethylaminopyridine (0.043 g) were added. The mixture was stirred at 60°C for 24 hrs. Ethyl acetate (100 mL) was added to the reaction mixture, triethylamine (1.19 mL), the mixture was stirred at room (0.422 g) in tetrahydrofuran was dropwise added pyridine pyridinecarboxylate dihydrochloride (1.08 g) obtained in (0.345 mL) under ice-cooling. After stirring under icemL), and (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2off and the filtrate was concentrated under reduced pyridyl]mcthyl]sulfinyl]-lH-benzimidazole (1.31 g), and the mixture was washed with water (100 mL) and cooling for 30 min., 2-(methylamino)ethyl temperature for 2 hrs.

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sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column

Crystallization from acetone-diethyl ether gave the title compound (0.9 g) as a white solid.

chromatography (eluted with ethyl acetate:hexane=4:1)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.22(3H,s), 3.16(3H,s), 3.80-4.20(2H,m), 4.38(2H,q,J=7.8Hz), 4.60-5.10(4H,m), 6.64(1H,d,J=5.8Hz),

8.14(1H, d, J=7.8Hz), 8.34(1H, d, J=5.8Hz), 8.75-8.79(1H, m).

7.29-7.40(2H,m), 7.47-7.52(2H,m), 7.81-7.89(2H,m),

10 Synthetic Example 13

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazol-1-yl]carbonyl]amino]ethyl methoxyacetate

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To a solution (15 mL) of bis(trichloromethyl) carbonate (0.652 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (C.55 mL) in tetrahydrofuran under icecooling. After stirring under ice-cooling for 30 min., 2-

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saturated brine (100 mL), dried over anhydrous sodium

The mixture was stirred at The saturated brine (30 mL) and dried over anhydrous magnesium After concentration under reduced pressure, the reduced pressure, ethyl acetate (80 mL) and water (50 mL) (R) -2ethyl acetate layer was separated and taken, washed with were added to the residue and the mixture was stirred. (methylamino)ethyl methoxyacetate (0.99 g) obtained in room temperature for 3 hrs. After concentration under residue was dissolved in tetrahydrofuran (15 mL). Reference Example 13 was added. sulfate.

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acetone:ethyl acetate=1:3), and further by basic silica gel triethylamine (0.86 mL) and 4-dimethylaminopyridine (0.037 under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate, then layer was separated and taken, and the ethyl acetate layer The ethyl acetate days. After concentration under reduced pressure, ethyl g) were added, and the mixture was stirred at 60°C for 4 carbonate solution (30 mL) and water (30 mL), and dried After concentration acetate (80 mL) and water (30 mL) were added to the was washed with a saturated aqueous sodium hydrogen oyridyl]methyl]sulfinyl]-lH-benzimidazole (1.13 g), column chromatography (eluted with ethyl residue, and the mixture was stirred. over anhydrous magnesium sulfate.

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(0.588 g) as coloriess syrup.

H-NMR (CDCL3): 2.32(3H,s), 2.68(3H,s), 3.48(3H,s), 3.69-

4.02(4H,m), 4.38(2H,q,J=7.8Hz), 4.67(2H,t,J=6.6Hz),

4.99(1H,d,J=13.9Hz), 5.12(1H,c,J=13.9Hz),

6.63(1H,d,J=5.7Hz), 7.29-7.46(2H,m), 7.62(1H,m),

7.81(1H,m), 8.25(1H,d,J=5.7Hz).

Synthetic Example 14

Ethyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

crifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-1H-

benzimidazol-1-yl]carbonyl]amino]ethyl carbonate 10

[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-

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To a solution (40 mL) of bis(trichloromethyl)carbonate sthyl 2-(methylamino)ethyl carbonate hydrochloride (2.02 g) A solution (2 (2 mL) of pyridine (1.07 mL) in tetrahydrofuran under ice-(1.31 g) in tetrahydrofuran was dropwise added a solution cooling. After stirring under ice-cooling for 10 min., mL) of triethylamine (1.84 mL) in tetrahydrofuran was obtained in Reference Example 14 was added.

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acetate: hexane=1:1, then 3:1) to give the title compound

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pressure, water (100 mL) was added to the residue, and the After concentration under reduced dropwise added and the mixture was stirred at room temperature for 1 hr.

ethyl acetate layer was washed with 0.2N hydrochloric acid anhydrous magnesium sulfate. After concentration under (50 mL) and saturated brine (100 mL) and dried over

reduced pressure, the residue was dissolved in

trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-10

tetrahydrofuran (50 mL). (R)-2-[[[3-Methyl-4-(2,2,2-

benzimidazole (3.69 g), triethylamine (2.09 mL) and 4-

dimethylaminopyridine (0.12 g) were added, and the mixture was stirred at 60°C for 6 hrs. and at room temperature for

8 hrs. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was

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extracted with ethyl acetate (100 mL). The ethyl acetate

layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration

under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl

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from diethyl ether and recrystallization from diethyl ether acetate:hexane=3:7, then ethyl acetate). Crystallization

"H-NMR(CDCl<sub>3</sub>): 1.32(3H, \(\capprox\), \(\J-7.2Hz\), \(\Int\). 2.23(3H, s), \(3.10(3H, bs)\), gave the title compound (3.84 g) as a colorless solid.

3.50-4.20(2H,br), 4.22(2H,q,J=7.2Hz), 4.39(2H,q,J=7.9Hz),

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1.45(2H,m), 4.80-5.15(2H,br), 6.65(1H,d,J=5.6Hz), 7.36-7.50(3H,m), 7.84(1H,d,J=7.8Hz), 8.35(1H,d,J=5.6Hz). Synthetic Example 15

Isopropyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2->>enzimidazol-1-yl]carbonyl]amino]ethyl carbonate trifluorcethoxy) -2-pyridyl]methyl]sulfinyl]-1H-

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mixture was extracted with ethyl acetate (100 mL).

To a solution (30 mL) of bis(trichloromethyl) carbonate (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-(0.50 g) in tetrahydrofuran was dropwise added a solution sopropyl 2-(methylamino)ethyl carbonate hydrochloride cooling. After stirring under ice-cooling for 1 hr., (0.99 g) obtained in Reference Example 15 was added. solution (1 mL) of triethylamine (0.70 mL) in

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of pyridine (0.40 mL) in tetrahydrofuran and a solution (1 Bis(trichloromethyl)carbonate (0.50 g), a solution (1 mL) tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr.

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colorless solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.31(6H,d,J=6.3Hz), 2.23(3H,s), 3.08(3H,bs), 3.40-4.30(2H,br), 4.37(2H,q,J=7.9Hz), 4.32-4.53(2H,m), 4.80-5.20(3H,m), 6.63(1H,d,J=5.7Hz), 7.35-7.50(3H,m),

7.83(1H, d, J=7.2Hz), 8.34(1H, d, J=5.7Hz).

ynthetic Example 16

Isopropyl 2-[methyl[[2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lHbenzimidazol-1-yl]carbonyl]amino]ethyl carbonate

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To a solution (20 mL) of bis(trichloromethyl) carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., isopropyl 2-(methylamino) ethyl carbonate hydrochloride (1.18 g) obtained in Reference Example 15 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at

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diisopropyl ether gave the title compound (0.58 g) as a

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dimethylaminopyridine (0.037 g) were added, and the mixture dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4was stirred at 60°C for 12 hrs. and at room temperature for ethyl acetate layer was washed with saturated brine (50 mL) The layer was 3 days. After concentration under reduced pressure, water acetone:hexane=1:3, then 3:2), and further by basic silica under reduced pressure, the residue was purified by flash acetate:hexane=3:7, then ethyl acetate). Crystallization concentrated under reduced pressure; and the residue was extracted with ethyl acetate (50 mL). The ethyl acetate After concentration under reduced layer was washed with saturated brine (50 mL) and dried mL) of triethylamine (0.70 mL) in tetrahydrofuran were over anhydrous magnesium sulfate. After concentration mixture was extracted with ethyl acetate (50 mL). The from diethyl ether and recrystallization from acetonesuccessively added and the mixture was stirred at room (2, 2, 2-trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-lHbenzimidazole (1.11 g), triethylamine (0.84 mL) and 4-The mixture was pressure, water (50 mL) was added to the residue. silica gel column chromatography (eluted with gel column chromatography (eluted with ethyl and dried over anhydrous magnesium sulfate. (50 mL) was added to the residue. temperature for 1 hr.

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reduced pressure, ethyl acetate (80 mL) and water (30 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (25 mL). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-

pyridyl]methyl]sulfinyl]-lH-benzimidazole (1.73 g),

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triethylamine (1.31 mL) and 4-dimethylaminopyridine (0.057 g) were added, and the mixture was stirred at 60°C for 5 hrs. After concentration under reduced pressure, ethyl acetate (100 mL) and water (50 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column. chromatography (eluted with ethyl acetate:hexane=1:1), and further by silica gel

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acetate:hexane=1:1, then 2:1). Crystallization from disopropyl ether-hexane and recrystallization from disopropyl ether gave the title compound (1.20 g) as a colorless solid.

column chromatography (eluted with ethyl

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25 <sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.31(6H, d, J=6.6Hz), 2.23(3H,s), 3.08(3H,bs),

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3.50-3.90(2H,bm), 4.38(2H,q,J=7.8Hz), 4.36-4.58(2H,bm),
4.79-5.15(3H,m), 6.64(1H,d,J=5.7Hz), 7.35-7.48(3H,m),
7.83(1H,d,J=7.5Hz), 8.34(1H,d,J=5.7Hz).

Synthetic Example 17

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Benzyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lHbenzimidazol-1-yl]carbonyl]amino]ethyl carbonate

To a solution (30 mL) of bis(trichloromethyl) carbonate (0.50 g) in tetranydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under icecoling. After stirring under ice-cooling for 1 hr., benzyl 2-(methylamino)ethyl carbonate hydrochloride (1.08 g) obtained in Reference Example 16 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred overnight at

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pressure, water (50 mL) was added to the residue. The

room temperature. After concentration under reduced

mixture was extracted with ethyl acetate (50 mL). The

ethyl acetate layer was washed with saturated brine (50 mL)

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5 and dried over anhydrous magnesium sulfate. The layer was

concentrated under reduced pressure, and the residue was

dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-

(2,2,2-trifluorcethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-

dimethylaminopyridine (0.037 g) were added, and the mixture

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was stirred overnight at 60°C. After concentration under reduced pressure, water (50 mL) was added to the residue.

reduced pressure, water (30 mL) was added to the residue.

The mixture was extracted with ethyl acetate (50 mL). The

ethyl acetate layer was washed with saturated brine (50 mL)

15 and dried over anhydrous magnesium sulfate. After

concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (eluted

with acetone:hexane=1:3, then 3:2). Crystallization from

acetone-diethyl ether and recrystallization from acetone-

20 diethyl ether gave the title compound (1.17 g) as a

colorless solid.

H-NMR(CDCl<sub>3</sub>): 2.22(3H,s), 3.05(3H,bs), 3.50-4.20(2H,br),

4.37(2H,q,J=7.8Hz), 4.46(2H,m), 4.80-5.10(2H,br),

5.17(2H,s), 6.62(1H,d,J=5.6Hz), 7.26-7.48(8H,m), 7.77-

Synthetic Example 18

2-{Methy1[[(R)-2-[[[3-methy1-4-(2,2,2-

trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

benzimidazol-1-yl]carbonyl]amino]ethyl tetrahydropyran-4-yl

carbonate

To a solution (20 mL) of bis(trichloromethyl)carbonate

(0.48 g) in tetrahydrofuran was dropwise added a solution

(1 ml) of pyridine (0.39 mL) in setrahydrofuran under ice-

cooling. After stirring under ice-cooling for 20 min., 2-(methylamino)ethyl tetrahydropyran-4-yl carbonate

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hydrochloride (0.96 g) obtained in Reference Example 17 was

added. A solution (1 mL) of triethylamine (0.67 mL) in

tetrahydrofuran was dropwise added, and the mixture was 15 stirred at room temperature for 2 hrs. After concentration

under reduced pressure, water (50 mL) was added to the

residue. The mixture was extracted with ethyl acetate (50

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7.88(1H,m), 8.33(1H,d,J=5.6Hz)

mL). The ethyl acetate layer was washed with 0.2N

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dimethylaminopyridine (0.042 g) were added, and the mixture dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4was stirred at 60°C for 6 hrs. and at room temperature for hydrochloric acid (20 mL) and saturated brine (50 mL) and 8 hrs. After concentration under reduced pressure, water under reduced pressure, the residue was purified by basic acetate:hexane=3:7, then ethyl acetate). Crystallization concentrated under reduced pressure, and the residue was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration dried over anhydrous magnesium sulfate. The layer was from diethyl ether and recrystallization from acetone-(2, 2, 2-trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-1Hbenzimidazole (1.26 g), triethylamine (0.71 mL) and silica gel column chromatography (eluted with ethyl disopropyl ether gave the title compound (1.45 g) The mixture was (50 mL) was added to the residue. colorless solid.

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2.23(3H,s), 3.09(3H,bs), 3.40-4.30(2H,br), 3.45-3.57(2H,m), 'H-NMR(CDCl<sub>3</sub>): 1.64-1.81(2H,m), 1.92-2.03(2H,m),

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3.87-3.97(2H,m), 4.38(2H,q,J=7.8Hz), 4.45(2H,m), 4.77-

5.15(3H,m), 6.64(1H,d,J=5.7Hz), 7.35-7.50(3H,m),

7.83(1H, d, J=6.9Hz), 8.35(1H, d, J=5.7Hz) 25

residue. The mixture was extracted with ethyl acetate (50

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Synthetic Example 19

2-Methoxyethyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2benzimidazol-1-yl]carbonyl]amino]ethyl carbonate trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lH-

To a solution (20 mL) of bis(trichloromethyl) carbonate (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under icecooling. After stirring under ice-cooling for 10 min., 2-After concentration (C.59 g) in tetrahydrofuran was dropwise added a solution methoxyethyl 2-(methylamino)ethyl carbonate hydrochloride tetrahydrofuran was dropwise added and the mixture was under reduced pressure, water (50 mL) was added to the (1.07 g) obtained in Reference Example 18 was added. solution (1 mL) of triethylamine (0.84 mL) in stirred at room temperature for 1 hr.

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dimethylaminopyridine (0.061 g) were added, and the mixture from ethyl acetate-diethyl ether and recrystallization from dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4was stirred at 60°C for 6 hrs. and at room temperature for saturated brine (50 mL) and water under reduced pressure, the residue was purified by basic acetate:hexane=3:7, then ethyl acetate). Crystallization concentrated under reduced pressure, and the residue was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried ethyl acetate-diisopropyl ether gave the title compound dried over anhydrous magnesium suifate. The layer was over anhydrous magnesium sulfate. After concentration (2,2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lHbenzimidazole (1.85 g), triethylamine (1.05 mL) and 4-After concentration under reduced pressure, silica gel column chromatography (eluted with ethyl mL). The ethyl acetate layer was washed with 0.2N The mixture was (50 mL) was added to the residue. hydrochloric acid (20 mL) and (1.39 g) as a colorless solid. 8 hrs.

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.23(3H,s), 3.09(3H,bs), 3.37(3H,s), 3.50-4.20(2H,br), 3.59-3.65(2H,m), 4.28-4.33(2H,m),

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4.38(2H,q,J=7.8Hz), 4.46(2H,m), 4.80-5.15(2H,br),

6.64(1H,d,J=5.7Hz), 7.35-7.47(3H,m), 7.83(1H,d,J=7.8Hz),

8.34 (1H, d, J=5.7Hz).

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Synthetic Example 20

2-[Ethyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)2-pyridyl]methyl]sulfinyl]-IH-benzimidazol-1-

yl]carbonyl]amino]ethyl acetate

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To a solution (30 mL) of bis(trichloromethyl) carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under icecoling. After stirring under ice-cooling for 10 min., 2-(ethylamino) ethyl acetate hydrochloride (0.67 g) obtained in Reference Example 2C was added. A solution (1 mL) of triethylamine (C.84 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in

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tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trif]]]]
trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazole (1.11 g), triethylamine (0.84 mL) and 4dimethylaminopyridine (0.037 g) were added, and the mixture
was stirred overnight at 60°C. After concentration under
reduced pressure, water (50 mL) was added to the residue.

The mixture was extracted with ethyl acetate (50 mL). The
ethyl acetate layer was washed with saturated brine (50 mL)
and dried over anhydrous magnesium sulfate. After

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concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate) to give the title compound (1.58 g) as a yellow amorphous solid.

<sup>1</sup>H-KMR(CDCl<sub>3</sub>): 1.25(3H,m), 2.08(3H,s), 2.23(3H,s), 3.30-4.10(4H,br), 4.23-4.45(2H,m), 4.38(2H,q,J=7.8Hz), 4.75-5.20(2H,br), 6.64(1H,d,J=5.7Hz), 7.35-7.46(3H,m), 7.84(1H,d,J=6.9Hz), 8.36(1H,d,J=5.7Hz).

Synthetic Example 21

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2-[Isopropyl[[(R)-2-[[[3-methyl-4-(2,2,2-20 trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lH-

benzimicazol-1-yl]carbonyl]amino]ethyl acetate

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To a solution (10 mL) of bis(trichloromethyl) carbonate edded to the residue. The mixture was extracted with ethyl (5 mL) of pyridine (0.445 mL) in tetrahydrofuran under ice-2 (0.543 g) in tetrahydrofuran was dropwise added a solution obtained in Reference Example 22 was added. A solution (5 added to a solution (20 mL) of (R)-2-[[[3-methyl-4-(2,2,2acetate (50 mL). The ethyl acetate layer was washed with obtained oil was dissolved in tetrahydrofuran (5 mL), and cooling, and the mixture was stirred at 0°C for 30 min. sulfate, and concentrated under reduced pressure. The mL) of triethylamine (0.805 mL) in tetrahydrofuran was concentrated under reduced pressure, water (30 mL) was 4saturated brine (30 mL), dried over anhydrous sodium benzimidazole (1.73 g), triethylamine (1.53 mL) and dropwise added, and the mixture was stirred at room (Isopropylamino)ethyl acetate hydrochloride (1.0 g) The reaction mixture was trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Htemperature for 30 min.

chromatography (eluted with ethyl acetate:hexane=2:1, then mixture was concentrated under reduced pressure and water layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced dimethylaminopyridine (0.134 g) in tetrahydrofuran. The extracted with ethyl acetate (50 mL). The ethyl acetate pressure. The residue was purified by silica gel column ethyl acetate) to give the title compound (1.50 g) as a mixture was stirred at 40°C for 12 hrs. The reaction (30 mL) was added to the residue. The mixture was pale-yellow amorphous solid.

H-NMR(CDCl<sub>3</sub>): 1.20-1.40(6H,m), 2.05(3H×0.4,s),

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2.11(3H×C.6,s), 2.18(3H×O.6,s), 2.27(3H×O.4,s), 3.40-

3.60(1H,m), 3.70-4.60(6H,m), 4.70-5.25(2H,m),

6.65(1H,d,J=5.8Hz), 7.30-7.50(3H,m), 7.75-7.90(1H,m), 15

8.37 (1H, d, J=5.8Hz).

Synthetic Example 22

Ethyl 2-[isopropyl[[(3)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl)methyl)sulfinyl)-1H-

benzimidazol-1-yl]carbonyl]amino]ethyl carbonate

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reaction mixture. A solution (5 mL) of triethylamine (0.69 To a solution (10 mL) of bis(trichloromethyl) carbonate (5 mL) of pyridine (0.381 mL) in tetrahydrofuran under ice-Ethyl 2-(isopropylamino)ethyl carbonate hydrochloride (1.0 mL) in tetrahydrofuran was dropwise added, and the mixture (0.467 g) in tetrahydrofuran was dropwise added a solution was stirred at 0°C for 15 min. and at room temperature for residue. The mixture was extracted with ethyl acetate (50 brine (30 mL), dried over anhydrous sodium sulfate, and ML). The ethyl acetate layer was washed with saturated cooling, and the mixture was stirred at 0°C for 30 min. g) obtained in Reference Example 23 was added to the The reaction mixture was concentrated under reduced pressure and water (30 mL) was added to the 30 min.

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concentrated under reduced pressure. The obtained oil was

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dissolved in tetrahydrofuran (5 mL), and added to a

solution (20 mL) of (R)-2-[[[3-methyl-4-(2,2,2-

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trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidzzole (1.48 g), triethylamine (1.32 mL) and 4dimethylaminopyridine (0.115 g) in tetranydrofuran, and the
mixture was stirred at 40°C for 12 hrs. The reaction
mixture was concentrated under reduced pressure and water
(30 mL) was added to the residue. The mixture was
extracted with ethyl acetate (50 mL). The ethyl acetate
layer was washed with saturated brine (30 mL), dried over
anhydrous sodium sulfate, and concentrated under reduced
pressure. The residue was purified by silica gel column
chromatography (eluted with ethyl acetate:hexane=2:1, then
ethyl acetate) to give the title compound (1.20 g) as a
pale-yellow amorphous solid.

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<sup>1</sup>H-NMR(CDCL<sub>3</sub>): 1.20-1.40(9H,m), 2.17(3H×0.6,s), 15 2.27(3H×0.4,s), 3.40-3.70(1H,m), 3.75-4.65(8H,m), 4.70-

7.90(1H,m), 8.38(1H,d,J=5.8Hz).

5.33(2H,m), 6.64(1H,d,J=5.8Hz), 7.35-7.55(3H,m), 7.75-

Synthetic Example 23

2-[Cyclohexyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluorocthoxy]-2-pyridyl]methyl]sulfinyl]-1H-

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benzimidazol-1-yl]carbonyl]amino]ethyl acetate

To a solution (10 mL) of bis(trichloromethyl) carbonate (0.593 g) in tetrahydrofuran was dropwise added pyridine (0.485 mL) under ice-cooling. After stirring under ice-cooling for 30 min., 2-(cyclohexylamino)ethyl acetate hydrochloride (1.33 g) obtained in Reference Example 25 was added. Triethylamine (0.84 mL) was dropwise added, and the mixture was stirred at room temperature for 2 hrs. Ethyl acetate (50 mL) was added to the reaction mixture and the mixture was washed with water (50 mL) and saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), and (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-

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pyridyl]methyl]sulfinyl]-lH-benzimidazole (1.61 g), triethylamine (1.21 mL) and 4-dimethylaminopyridine (0.053 g) were added. The mixture was stirred at 60°C for 24 hrs. Ethyl acetate (50 mL) was added to the reaction mixture, and the mixture was washed with water (20 mL) and saturated

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purified by flash silica gel column chromatography (eluted with ethyl acetate:hexane=1:4, then ethyl acetate) to give brine (50 mL), dried over anhydrous sodium sulfate, and the title compound (2.12 g) as a pale-yellow amorphous The residue was concentrated under reduced pressure.

H-NMR(CDCl<sub>3</sub>): 1.00-2.42(16H,m), 3.30-3.70(2H,m), 3.80-4.00(1H,m), 4.27-4.42(2H,m), 4.40(2H,q,J=8.2Hz),

4.78(1H×C.5,d,J=13:2Hz), 4.97(2H×0.5,s),

5.20(1H×C.5, d, J=13.2Hz), 6.67(1H, d, J=5.8Hz), 7.36-7.46(3H,m), 7.81-7.91(1H,m), 6.39(1H,d,J=5.8Hz).

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Synthetic Example 24

benzimidazol-1-yljcarbonyl]amino]ethyl ethyl carbonate 2-[Cyclohexyl[[(R)-2-[[[3-methy1-4-(2,2,2trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-1H-

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To a solution (10 mL) of bis(trichloromethyl) carbonate (0.238 g) in tetrahydrofuran was dropwise added pyridine

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the reaction mixture, and the mixture was washed with water cemperature for 2 hrs. Ethyl acetate (50 mL) was added to (50 mL) and saturated brine (50 mL), dried over anhydrous nagnesium sulfate and concentrated under reduced pressure. carbonate hydrochloride (0.605 g) obtained in Reference (0.20 mL) under ice-cooling. After stirring under icesooling for 30 min., 2-(cyclohexylamino)ethyl ethyl Triethylamine (0.335 mL) was dropwise added, and the mixture was stirred at room Example 26 was added. 10

g) were added. The mixture was stirred at 60°C for 24 hrs. The residue was dissolved in tetrahydrofuran (10 mL), and triethylamine (0.45 mL) and 4-dimethylaminopyridine (0.02 pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.60 g), (R)-2-[[[3-methy1-4-(2,2,2-trifluoroethoxy)-2-

and the mixture was washed with water (20 mL) and saturated purified by flash silica gel column chromatography (eluted with ethyl acetate:hexane=1:4, then ethyl acetate) to give Ethyl acetate (50 mL) was added to the reaction mixture, orine (50 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was

the title compound (0.92 g) as a pale-yellow amorphous 20

H-NMR(CDCl<sub>3</sub>): 1.02-2.27(16H,m), 3.40-4.60(9H,m),

4.78(1H×0.5,d,J=13.2Hz), 4.97(2H×0.5,s),

5.44(lH×0.5,d,J=13.2Hz), 6.69(lH,d,J=5.6Hz), 7.32-25

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7.54(3H,m), 7.80-7.91(1H,m), 8.38(1H,d,J= 5.6Hz). Synthetic Example 25 2-[[[(R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

yl]carbonyl](phenyl)amino]ethyl acetate

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To a solution (350 mL) of

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sulfate and concentrated under reduced pressure to give 2bis(trichloromethyl)carbonate (13.4 g) in tetrahydrofuran temperature for 2 hrs. After concentration under reduced was dropwise added pyridine (10.38 mL) under ice-cooling. saturated brine (500 mL), dried over anhydrous magnesium pressure, ethyl acetate (500 mL) and water (500 mL) were ethyl acetate layer was separated and taken, washed with Reference Example 27 was added. Triethylamine (18.4 mL) anilinoethyl acetate hydrochloride (25.9 g) obtained in was dropwise added, and the mixture was stirred at room added to the residue, and the mixture was stirred. After stirring under ice-cooling for 30 min., 2-

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(chlorocarbonyl) (phenyl) amino]ethyl acetate. This was

dissolved in tetrahydrofuran (300 mL), (R)-2-[[[3-methyl-4-(2,2,2,2-trifluoroethoxy)-2-pyricyl]methyl]sulfinyl]-1H-

dimethylaminopyridine (1.363 g) were added, and the mixture benzimidazole (41.2 g), triethylamine (15.6 mL) and 4-

nL), dried over anhydrous sodium sulfate, and concentrated The residue was purified by basic was stirred at 60°C for 3 hrs. Ethyl acetate (800 mL) was added to the reaction mixture, and the mixture was washed diethyl ether gave the title compound (54.1 g) as a white twice with water (800 mL) and with saturated brine (800 Crystallization from silica gel column chromatography (eluted with ethyl scetate:hexane=3:7, then 1:1). under reduced pressure. solid.

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H-NMR(CDCl3): 2.00(3H,s), 2.25(3H,s), 4.15-4.48(6H,m), 1.83(1H, d, J=13.6Hz), 5.05(1H, d, J=13.6Hz),

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6.67(1H,d,J=5.4Hz), 7.03-7.45(8H,m), 7.64-7.69(1H,m), 3.40(1H, d, J=5.4Hz).

Synthetic Example 26

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2-[[[2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2oyridyl]methyl]sulfinyl]-1H-benzimidazol-1yl]carbonyl](phenyl)amino]ethyl acetate

To a solution (10 mL) of 2-

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column chromatography (eluted with acetone:hexane=1:4, then with water (50 mL) and saturated brine (50 mL), dried over prepared in the same manner as in Synthetic Example 25 in added to the reaction mixture, and the mixture was washed anhydrous sodium sulfate, and concentrated under reduced 4-3:2). Crystallization from diethyl ether gave the title pressure. The residue was purified by flash silica gel stirred at 60°C for 15 hrs. Ethyl acetate (30 mL) was benzimidazole (0.739 g), triethylamine (0.558 mL) and [(chlorocarbonyl)(phenyl)amino]ethyl acetate (0.58 g) cimethylaminopyridine (0.024 g), and the mixture was tetrahydrofuran were added 2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hcompound (0.779 g) as a white solid.

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Synthetic Example 27 8.40(1H, d, J=5.8Hz).

tert-Butyl [2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2benzimidazol-1-yl]carbonyl]amino]-3-pyridyl]methyl trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

carbonate

To a solution (20 mL) of bis(trichloromethyl) carbonate temperature for 2 hrs. The precipitated solid was filtered pressure. The residue was dissolved in tetrahydrofuran (20 triethylamine (0.70 mL) and 4-dimethylaminopyridine (0.031 Example 28 was added, and the mixture was stirred at room (0.30 g) in tetrahydrofuran was dropwise added pyridine pyridyl]methyl carbonate (0.71 g) obtained in Reference (0.24 mL) under ice-cooling. After stirring under iceoff and the filtrate was concentrated under reduced ml), (R)-2-[[[3-methy1-4-(2,2,2-trifluoroethoxy)-2pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.92 g), cooling for 36 min., tert-butyl [2-(methylamino)-3-

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 $^{1}$ H-NMR(CDC13): 1.99(3H,s), 2.25(3H,s), 4.20-4.48(6H,m),

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6.67(1H, d, J=5.8Hz), 7.03-7.45(8H, m), 7.64-7.69(1H, m),

4.83(1H, d, J=13.6Hz), 5.05(1H, d, J=13.6Hz),

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g) were added, and the mixture was stirred at 60°C for 1 hr. Water (50 mL) was added to the reaction mixture and the mixture was extracted twice with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:2), and further by basic silica gel column chromatography (eluted with ethyl acetate) to give the title compound (0.38 g) as a pale-yellow amorphous solid.

<sup>1</sup>H-NWR (CDCl<sub>3</sub>): 1.46(9H,s), 2.25(3H,s), 3.54(3H,s),
4.37(2H,q,J=8.0Hz), 4.95(2E,s), 5.15(1H,d,J=14.0Hz),
5.27(1H,d,J=14.0Hz), 8.33(1H,d,J=5.4Hz), 8.44-8.46(1H,m).

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2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lHbenzimidazol-1-yl]carbonyl]amino]benzyl acetate

Synthetic Example 28

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To a solution (30 mL) of bis(trichloromethyl)carbonate

ethyl acetate (100 mL). The ethyl acetate layer was washed cooling for 30 min., 2-(methylamino)benzyl acetate (2.57 g) to the reaction mixture, and the mixture was extracted with dimethylaminopyridine (0.15 g) were added, and the mixture with saturated brine (100 mL), dried over anhydrous sodium dissolved in tetrahydrofuran (40 mL), (R)-2-[[[3-methyl-4-Water (100 mL) was added obtained in Reference Example 29 was added. The mixture precipitated solid was filtered off and the filtrate was (1.46 g) in tetrahydrofuran was dropwise added pyridine After stirring under icebenzimidazole (4.41 g), triethylamine (3.33 mL) and 4-[2, 2, 2-trifluoroethoxy] -2-pyridyl]methyl]sulfinyl]-lH-The residue was The was stirred at room temperature for 3 hrs. concentrated under reduced pressure. was stirred at 60°C for 18 hrs. (1.16 mL) under ice-cooling. 10 15

gave the title compound (2.76 g) as a white solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 2.10(3H, s), 2.00-2.30(3H, bx), 3.203.50(3H, bx), 4.38(2H, q, J=7.6Hz), 4.70-5.20(2H, m), 5.205.50(2H, m), 6.65(1H, d, J=5.4Hz), 7.10-7.82(8H, m),
8.38(1H, d, J=5.4Hz).

chromatography (eluted with acetone:hexane=1:4, then 1:2).

sulfate, and concentrated under reduced pressure.

residue was purified by flash silica gel column

Crystallization from ethyl acetate-diethyl ether-hexane

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Synthetic Example 29

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2-[[2-(Acetyloxy)ethyl][[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazol-1-yl]carbonyl]amino]ethyl acetate

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To a solution (30 mL) of bis(trichloromethyl) carbonate temperature for 2 hrs. The precipitated solid was filtered (R)-2-[[[3-Methy1-4-[(2-acetyloxyethyl)amino]ethyl acetate hydrochloride (1.13 (1 ml) of pyridine (0.40 ml) in tetrahydrofuran under icecooling. After stirring under ice-cooling for 10 min., 2pressure. Ethyl acetate (20 mL) was added to the residue, (0.50 g) in tetrahydrofuran was dropwise added a solution was concentrated under reduced pressure. The residue was the precipitated solid was filtered off and the filtrate (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was (2, 2, 2-trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-1Hdropwise added, and the mixture was stirred at room off and the filtrate was concentrated under reduced g) obtained in Reference Example 30 was added. dissolved in tetrahydrofuran (30 mL).

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and 4dimethylaminopyridine (catalytic amount) were added, penzimidazole (1.48 g), triethylamine (1.12 mL) and After the mixture was stirred at 60°C overnight.

IL), activated carbon was added and the mixture was stirred added to the residue. The mixture was extracted with ethyl eluted with ethyl acetate:hexane=1:1, then ethyl acetate), (eluted with ethyl acetate:hexane=1:1, then ethyl acetate). saturated brine (50 mL) and dried over anhydrous magnesium acetate (50 mL). The ethyl acetate layer was washed with sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography The resulting product was dissolved in ethyl acetate (20 and further by basic silica gel column chromatography concentration under reduced pressure, water (50 mL) ഗ 2 15

overnight. The activated carbon was filtered off and the filtrate was concentrated under reduced pressure to give the title compound (1.60 g) as a yellow amorphous solid. H-NMR(CDCl<sub>3</sub>): 2.06(3H,s), 2.08(3H,s), 2.24(3H,s), 3.40-4.15(8H,m), 4.39(2H,q,J=7.9Hz), 4.88(1H,d,J=13.2Hz),

5.05(1H,d,J=13.2Hz), 6.66(1H,d,J=5.6Hz), 7.38-7.50(3H,m), 7.87(1H,d,J=6.9Hz), 8.36(1H,d,J=5.6Hz). 20

Synthetic Example 30

[(2S)-1-[[(R)-2-[[[3-Methyl-4-(2,2,2-triflucroethoxy)-2-pyridyl]methyl]sulfinyl]-lH-benzimidazol-1-yl]carbonyl]-2-pyrrolidinyl]methyl acetate

To a solution (30 mL) of bis(trichloromethyl) carbonate dimethylaminopyridine (0.037 g) were added, and the mixture (R) -2-[[[3-Methyl-4was stirred at 60°C for 1 day and at room temperature for 2 A solution (1 mixture was extracted with ethyl acetate (50 mL) and dried (1 mL) of pyridine (3.40 mL) in tetrahydrofuran under ice-(S) (0.50 g) in tetrahydrofuran was dropwise added a solution temperature for 2 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue, and the concentrated under reduced pressure, and the residue was days. After concentration under reduced pressure, water (2, 2, 2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazole (1.11 g), triethylamine (0.84 mL) and 4cooling. After stirring under ice-cooling for 1 hr., mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room 2-pyrrolidinylmethyl acetate hydrochloride (0.90 g) over anhydrous magnesium sulfate. The layer was obtained in Reference Example 31 was added. dissolved in tetrahydrofuran (20 mL).

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icetate:hexane=3:1, then ethyl acetate, then acetone:ethyl acetate=1:4, then 2:3) to give the title compound (0.80 g) under reduced pressure, the residue was purified by basic The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration ģ (50 mL) was added to the residue and the mixture was acetate:hexane=1:1, then ethyl acetate) and further silica gel column chromatography (eluted with ethyl silica gel column chromatography (eluted with ethyl extracted with ethyl acetate (50 mL). as a pale-yellow amorphous solid. ß 10

3.39(1H,m), 3.50-3.62(1H,m), 4.20-4.45(4H,m), 4.58(1H,m) H-NMR(CDCl3): 1.80-2.30(4H,m), 2.09(3H,s), 2.30(3H,s), 1.89(1H,d,J=13.5Hz), 4.96(1H,d,J=13.5Hz),

6.65(1H, d, J=5.9Hz), 7.36-7.48(3H, m), 7.89(1H, d, J=8.7Hz), 8.38(1H, d, J=5.9Hz). 15

Synthetic Example 31

Ethyl [methyl[[(R)-2-[[[3-methyl-4-(2,2,2-:rifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

benzimicazol-l-yl]carbonyl]amino]acetate 20

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To a solution (30 mL) of bis(trichloromethyl) carbonate (50 mL). The ethyl acetate layer was washed with saturated After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (33 mL). (R)-2-[[[3-Methyl-4-(catalytic amount) were added, and the mixture was stirred (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-(0.50 g) in tetrahydrofuran was dropwise added a solution residue, and the mixture was extracted with ethyl acetate benzimidazole sodium (1.37 g) and 4-dimethylaminopyridine brine (50 mL) and dried over anhydrous magnesium sulfate. solid was filtered off and the filtrate was concentrated sarcosine ethyl ester hydrochloride (0.77 g) was added. stirred at room temperature for 1 hr. The precipitated under reduced pressure. Water (50 mL) was added to the cooling. After stirring under ice-cooling for 30 min., tetrainydrofuran was dropwise added and the mixture was (2,2,2-trifluoroethoxy) $^-2$ -pyridyl]methyl]sulfinyl] $^-1$ H $^$ solution (1 mL) of triethylamine (0.70 mL) in

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Synthetic Example 32

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To a solution (10 mL) of bis(trichloromethyl)carbonate (0.344 g) in tetrahydrofuran was dropwise added a solution

(5 mL) of pyridine (0.281 mL) in tetrahydrofuran under icecooling, and the mixture was stirred at  $0^{\circ}\text{C}$  for 30 min. (Methylamino) ethyl benzoate hydrochloride (0.750 g) S

5 obtained in Reference Example 5 was added. A solution mL) of triethylamine (0.485 mL) in tetrahydrofuran was

at added, and the mixture was stirred at 0°C for 1 hr. and room temperature for 30 min. The reaction mixture was

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concentrated under reduced pressure and water (30 mL) was

added to the residue. The mixture was extracted with ethyl

acetate (50 mL). The ethyl acetate layer was washed with

sulfate, and concentrated under reduced pressure. The saturated brine (30 mL), dried over anhydrous sodium

obtained oil was dissolved in tetrahydrofuran (5 mL), added 12

to a solution (10 mL) of 5-methoxy-2-[[(4-methoxy-3,5-

dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzoimidazole (1.0 g), triethylamine (0.808 mL) and 4-dimethylaminopyridine

(0.071 g) in tetrahydrofuran, and the mixture was stirred

The reaction mixture was concentrated at 40°C for 18 hrs. 20

residue. The mixture was extracted with ethyl acetate (50 was added to the under reduced pressure and water (30 mL)

mL). The ethyl acetate layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and

The residue was

concentrated under reduced pressure.

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ethyl acetate:hexane=1:1, then ethyl acetate) to give a 1:1 purified by silica gel column chromatography (eluted with

mixture (1.50 g) of the title compound and 2-[[[6-methoxy-

penzoimidazol-1-yl]carbonyl] (methyl) amino]ethyl benzoate as 2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-lHa pale-yellow amorphous solid.

'H-NMR(CDCl<sub>3</sub>): 2.05-2.35(6H,m), 3.00-3.30(3H,br), 3.60-4.40(8H,m), 4.60-5.10(4H,m), 6.80-7.00(2H,m), 7.20-

Synthetic Example 33 10

7.70(4H,m), 7.95-8.25(3H,m).

3-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

>>enzimidazol-1-yl]carbonyl]amino]propyl benzoate trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

To a solution (20 mL) of bis(trichloromethyl) carbonate (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-(0.582 g) in tetrahydrofuran was dropwise added a solution

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dimethylaminopyridine (0.054 g) were added, and the mixture The ethyl acetate layer was washed with saturated brine (30 ethyl acetate layer was washed with saturated brine (25 mL) dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-A solution (1 The layer was temperature for 2 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the was stirred at 60°C for 4 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, cooling. Aiter stirring under ice-cooling for 1 hr., 3concentrated under reduced pressure, and the residue was and the mixture was extracted with ethyl acetate (80 mL). After mixture was extracted with ethyl acctate (80 mL). The (2, 2, 2-trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-iHbenzimidazole (1.63 g), triethylamine (1.23 mL) and 4-ML) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room (methylamino)propyl benzoate hydrochloride (1.38 g) mL) and dried over anhydrous magnesium sulfate. obtained in Reference Example 32 was added. and dried over anhydrous magnesium sulfate.

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reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL).

The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (1.26 g) as a yellow amorphous solid.

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 $^{1}$ H-NMR(CDCl<sub>3</sub>): 2.21(3H,s), 2.20-2.30(2H,bm), 3.06(3H,bs),

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3.60-3.75(2H,bm), 4.36(2H,q,J=7.8Hz), 4.30-4.50(2H,bm), 4.80-5.15(2H,bm), 6.62(1H,d,J=5.7Hz), 7.26-7.44(5H,m), 7.54(1H,m), 7.81(1H,m), 7.93-8.03(2H,bm),

Synthetic Example 34

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8.35(1H, d, J=5.7Hz).

2-[Methy1[[2-[[[3-methy1-4-(2,2,2-trifluoroethoxy)-2pyridy1]methy1]sulfiny1]-1H-benzimidazol-1-

yl]carbonyl]aminojethyl tetrahydropyran-4-yl carbonate

To a solution (20 mL) of bis(trichloromethyl) carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 2C min., 2-(methylamino) ethyl tetrahydropyran-4-yl carbonate hydrochloride (1.43 g) obtained in Reference Example 17 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was

The ethyl acetate layer was washed with saturated dimethylaminopyridine (0.027 g) were added, and the mixture stirred at room temperature for 3 hrs. After concentration residue, and the mixture was extracted with ethyl acetate brine (20 mL), dried over anhydrous magnesium sulfate and residue, and the mixture was extracted with ethyl acetate dissolved in tetrahydrofuran (20 mL). 2-[[[3-Methyl-4under reduced pressure, water (30 mL) was added to the (2, 2, 2-trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-lHbenzimidazole (1.63 g), triethylamine (1.23 mL) and 4under reduced pressure, water (50 mL) was added to the was stirred at 60°C for 17.5 hrs. After concentration concentrated under reduced pressure. The residue was (120 mL). The ethyl acetate layer was washed with (80 mL).

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1:1), then by silica gel column chromatography (eluted with saturated brine (30 mL) and dried over anhydrous magnesium chromatography (eluted with ethyl acetate:hexane=1:2, then ethyl acetate:hexane=1:1, then 2:1). Crystallization from After concentration under reduced pressure, the a S residue was purifiec by basic silica gel column diethyl ether gave the title compound (1.23 g) colorless solid. sulfate. 15 20

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 $^{1}$ H-NM3(CDCl<sub>3</sub>): 1.64-1.81(2H,m), 1.92-2.03(2H,m),

2.23(3H,s), 3.10(3H,bs), 3.40-4.30(2H,br), 3.46-3.59(2H,m),

3.87-3.99(2H,m), 4.39(2H,q,J=7.9Hz), 4.45(2H,m), 4.77-

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5.15(3H,m), 6.65(1H,d,J=5.4Hz), 7.35-7.50(3H,m),

7.85(1H,m), 8.36(1H,d,J=5.4Hz)

Synthetic Example 35

Ethyl 2-[methyl[[2-[[[3-methyl-4-(2,2,2-

>>enzimidazol-1-yl]carbonyl]amino]ethyl carbonate trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

To a solution (20 mL) of bis (trichloromethyl) carbonate thyl 2-(methylamino)ethyl carbonate hydrochloride (1.10 g) (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-(0.582 g) in tetrahydrofuran was dropwise added a solution A solution (1 semperature for 3 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the cooling. After stirring under ice-cooling for 30 min., mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room mixture was extracted with ethyl acetate (80 mL). obtained in Reference Example 14 was added.

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The ethyl acetate layer was washed with saturated brine (30) ethyl acetate layer was washed with saturated brine (30 mL) purified by basic silica gel column chrometography (eluted and dried over anhydrous magnesium sulfate. The layer was dimethylaminopyridine (0.054 g) was added, and the mixture After concentration under and the mixture was extracted with ethyl acetate (100 mL). reduced pressure, water (40 mL) was added to the residue, to give the title compound concentrated under reduced pressure, and the residue was 2-[[[3-Methyl-4-(2, 2, 2-trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-lHwith ethyl acetate:hexane=1:2, then 1:1), and then by concentration under reduced pressure, the residue was benzimidazole (1.63 g), triethylamine (1.23 mL), 4silica gel column chromatography (eluted with ethyl mL), and dried over anhydrous magnesium sulfate. dissolved in tetrahydrofuran (20 mL). was stirred at 60°C for 14 hrs. acetate:hexane=1:1, then 2:1)

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.32(3H,t,J=7.1Hz), 2.23(3H,s), 3.09(3H,bs), 3.50-4.76(4H,br), 4.21(2H,q,J=7.1Hz), 4.38(2H,q,J=7.9Hz), 4.84-5.14(2H,m), 6.64(1H,d,J=5.6Hz), 7.36-7.46(3H,m), 7.83(1H,d,J=5.6Hz).

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(1.27 g) as a yellow amorphous solid.

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Ethyl 2-[methyl[[(S)-2-[[[3-methyl-4-(2,2,2-

trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lH-

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>>enzimidazol-1-yl]carbonyl]amino]ethyl carbonate

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To a solution (20 mL) of bis(trichloromethyl) carbonate cooling. After stirring under ice-cooling for 1 hr., ethyl (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-The layer (0.582 g) in tetrahydrofuran was dropwise added a solution obtained in Reference Example 14 was added. A solution (1 temperature for 2 hrs. After concentration under reduced pressure, water (30 ml) was added to the residue, and the was concentrated under reduced pressure, and the residue ethyl acetate layer was washed with saturated brine (30 (S)-2-[[[3mL) of triethylamine (0.84 mL) in tetrahydrofuran was 2-(methylamino)ethyl carbonate hydrochloride (1.10 g) dropwise added, and the mixture was stirred at room mixture was extracted with ethyl acetate (80 mL). mL), and dried over anhydrous magnesium sulfate. was dissolved in tetrahydrofuran (20 mL). Methyl-4-(2,2,2-trifluoroethoxy)-2-

pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.15 g),

triethylamine (0.87 mL) and 4-dimethylaminopyridine (0.035 g) were added, and the mixture was stirred at 60°C for 12 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (30 mL), and dried over anhydrous magnesium sulate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1). Crystallization from diethyl ether gave the title compound (0.40 g) as a colorless solid.

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1h-NMR(CDCl<sub>3</sub>): 1.32(3H,t,J=7.2Hz), 2.23(3H,s), 3.10(3H,bs),
3.50-4.56(4H,br), 4.22(2H,q,J=7.2Hz), 4.38(2H,q,J=7.9Hz),
4.84-5.14(2H,m), 6.65(1H,d,J=5.6Hz), 7.34-7.50(3H,m),
7.85(1H,m), 8.36(1H,d,J=5.6Hz).
Synthetic Example 37

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temperature for 2.5 hrs. After concentration under reduced To a solution (20 nL) of bis(trichloromethyl) carbonate sthyl 2-(methylamino)ethyl carbonate hydrochloride (1.10 g) ethyl acetate layer was washed with saturated brine  $(30\,$  mJ,)(1 mL) of pyridine (0.485 mL) in tetrahydrofuran under iceobtained in Reference Example 14 was added. A solution (1 (0.582 g) in tetrahydrofuran was dropwise added a solution The Layer was pressure, water (30 mL) was added to the residue, and the concentrated under reduced pressure, and the residue was 5-Methoxy-2-[[(4min., mixture was extracted with ethyl acetate (80 mL). The mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-iHcooling. After stirring under ice-cooling for 30 and dried over anhydrous magnesium sulfate. dissolved in tetrahydrofuran (20 mL).

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imidazo[4,5-b]pyridine (1.44 g) synthesized by the method

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described in JP-A-63-146882, triethylamine (1.16 mL) and 4-dimethylaminopyridine (C.049 g) were added, and the mixture was stirred at 60°C for 6 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous megnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1). Crystallization from diethyl ether gave the title compound (0.721 g) as a colorless solid.

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'H-NMR(CDCl<sub>3</sub>): 1.25-1.34(3H,m), 2.23(6H,s), 3.15,3.32(total 3H,s), 3.72(3H,s), 3.90-4.53(9H,m), 4.86(1H,d,J=13.4Hz), 4.95(1H,d,J=13.4Hz), 6.79(1H,d,J=8.7Hz), 7.95(1H,d,J=8.7Hz), 8.22(1H,s).

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Synthetic Example 38

2-[[[5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3yl]carbonyl](methyl)amino]ethyl acetate

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H<sub>3</sub>C-N H<sub>3</sub>C-OH<sub>3</sub> To a solution (20 mL) of bis(trichloromethyl) carbonate (methylamino)ethyl acetate hydrochloride (0.922 g) obtained (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-(0.582 g) in tetrahydrofuran was dropwise added a solution cooling. After stirring under ice-cooling for 30 min., 2added, and the mixture was stirred at room temperature for b]pyridine (0.85 g) synthesized by the method described in 2 hrs. After concentration under reduced pressure, water extracted with ethyl acetate (80 mL). The ethyl acetate rriethylamine (0.84 mL) in tetrahydrofuran was dropwise layer was washed with saturated brine (30 mL) and dried in Reference Example 2 was added. A solution (1 mL) of cetrahydrofuran (10 mL). 5-Methoxy-2-{{(4-methoxy-3,5over anhydrous magnesium sulfate. After concentration 30 mL) was added to the residue, and the mixture was under reduced pressure, the residue was dissolved in dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-JP-A-63-146882, triethylamine (0.70 mL) and 4-

dimethylaminopyridine (0.025 g) were added, and the mixture The ethyl acetate layer was washed with saturated brine (30 purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1). Crystallization from diethyl ether gave the title compound (0.173 g) as a and the mixture was extracted with ethyl acetate (90 mL). After concentration under reduced pressure, water (30 mL) was added to the residue, mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was was stirred at 60°C for 5 hrs. colcriess solid.

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H-NMR(CDC13): 2.04,2.09(total 3H,s), 2.24(6H,s),

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3.13,3.30(total 3H,s), 3.45-3.97(2H,m), 3.72(3H,s)

3.97(3H,s), 4.15-4.50(2H,m), 4.85(1H,d,J=13.1Hz),

4.96(1H,d,J=13.1Hz), 6.80(1H,d,J=8.9Hz), 7.96(1H,d,J=8.9Hz), 8.22(IH,s). 15

Synthetic Example 39

pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-2-[[[5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2yl]carbonyl](phenyl)amino]ethyl acetate

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To a solution (10 mL) of bis(trichloromethyl)carbonate (1 mL) of pyridine (0.243 mL) in tetrahydrofuran under ice-(0.291 g) in tetranydrofuran was dropwise added a solution cooling. After stirring under ice-cooling for 30 min., 2added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water rriethylamine (0.419 mL) in tetrahydrofuran was dropwise extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration anilinoethyl acetate hydrochloride (0.647 g) obtained (20 mL) was added to the residue, and the mixture was Reference Example 27 was added. A solution (1 mL) of under reduced pressure, the residue was dissolved in

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b)pyridine (0.867 g) synthesized by the method described in cetrahydrofuran (10 mL). 5-Methoxy-2-[[(4-methoxy-3,5dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-JP-A-63-146882, triethylamine (0.697 mL) and 4-

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The ethyl acetate layer was washed with saturated brine (15 purified by basic silica gel column chromatography (eluted dimethylaminopyridine (0.020 g) was added, and the mixture After concentration under reduced pressure, water  $(20~\mathrm{mL})$  was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). nL) and cried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was with ethyl acetate:hexane=1:1). Crystallization from diethyl ether gave the title compound (0.311 g) as a was stirred at 60°C for 10 hrs. colorless solid.

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3.72(3H,s), 4.01(3H,s), 4.12-4.52(4H,m), 4.78-5.22(2H,m), 5.62(1H,d,J=8.7Hz), 7.02-7.18(3H,m), 7.32-7.48(2H,m), H-NMR(CDCl<sub>3</sub>): 1.96(3H,s), 2.23(3H,s), 2.25(3H,s),

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7.73(1H, d, J=8.7Hz), 8.26(1H,s).

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Synthetic Example 40

trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazol-1-yl]carbonyl]amino]butyl acetate 4-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

To a solution (20 mL) of bis(trichloromethyl)carbonate dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(methylamino)butyl acetate hydrochloride (1.08 g) obtained (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under icecooling. After stirring under ice-cooling for 30 min., 4added, and the mixture was stirred at room temperature for (0.59 g) in tetrahydrofuran was dropwise added a solution 3 hrs. After concentration under reduced pressure, water in Reference Example 37 was added. A solution (1 mL) of The ethyl acetate concentrated under reduced pressure, and the residue was triethylamine (0.84 mL) in tetrahydrofuran was dropwise layer was washed with saturated brine (50 mL) and dried (2, 2, 2-trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-lH-50~mL) was added to the residue and the mixture was over anhydrous magnesium sulfate. The layer was extracted with ethyl acetate (50 mL). 15

ethyl acetate (50 mL). The ethyl acetate layer was washed dimethylaminopyridine (catalytic amount) were added, and added to the residue and the mixture was extracted with concentration under reduced pressure, water (50 mL) was penzimidazole (1.02 g), triethylamine (0.77 mL) and 4pressure, the residue was purified by basic silica gel magnesium sulfate. After concentration under reduced with saturated brine (50 mL) and dried over anhydrous the mixture was stirred at 60°C cvernight. After

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acetate:hexane=1:2, ther 1:1) to give the title compound 4.37(2H,q,J=7.8Hz), 4.85-5.13(2H,m), 6.64(1H,d,J=5.6Hz), H-NMR(CDCl<sub>3</sub>): 1.65-1.85(4H,m), 2.03(3H,s), 2.23(3H,s), 3.02(3H,bs), 3.45-3.63(2H,m), 4.03-4.13(2H,m), (0.93 g) as a yellow amorphous solid.

column chromatography (eluted with ethyl

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7.36-7.46(3H,m), 7.84(1H,d,J=8.4Hz), 8.35(1H,d,J=5.6Hz) Synthetic Example 41

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Ethyl 4-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2benzimidazol-1-yl]carbonyl]amino]butyl carbonate trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

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To a solution (20 mL) of bis(trichloromethyl) carbonate ethyl 4-(methylamino)butyl carbonate hydrochloride (1.27 g) (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under iceobtained in Reference Example 39 was added. A solution (1 (0.59 g) in tetrahydrofuran was dropwise added a solution cooling. After stirring under ice-cooling for 30 min., mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room

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(R)-2-[[[3-Methyl-4ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was temperature for 3 hrs. After concentration under reduced concentrated under reduced pressure, and the residue was pressure, water (50 mL) was added to the residue and the (2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hmixture was extracted with ethyl acetate (50 mL). dissolved in tetrahydrofuran (20 mL).

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and benzimidazole (1.26 g), triethylamine (0.95 mL) and 4dimethylaminopyridine (catalytic amount) were added, the mixture was stirred at 60°C overnight. After 266

ethyl acetate (50 mL). The ethyl acetate layer was washed acetate:hexane=1:2, then 1:1) to give the title compound concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with pressure, the residue was purified by basic silica gel with saturated brine (50 ml) and dried over anhydrous magnesium sulfate. After concentration under reduced column chromatography (eluted with ethyl (1.08 g) as a yellow amorphous solid.

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2.23(3H,s), 3.01(3H,bs), 3.50-3.62(2H,m), 4.15-4.22(4H,m), 4.38(2H,q,J=7.8Hz), 4.87-5.13(2H,m), 6.64(1H,d,J=5.4Hz), 7.35-7.46(3H,m), 7.83(1H,d,J=7.8Hz), 8.35(1H,d,J=5.4Hz). 'H-NMR(CDCl<sub>3</sub>): 1.31(3H,t,J=7.2Hz), 1.73-1.91(4H,m), Synthetic Example 42

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benzimidazol-1-yl]carbonyl]amino]propyl carbonate Ethyl 3-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy>-2-pyridyl]methyl]sulfinyl]-1H-

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To a solution (20 mL) of bis(trichloromethyl) carbonate dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4ethyl acetate layer was washed with saturated brine (50 mL) The layer was g) obtained in Reference Example 44 was added. A solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under 1cesthyl 3-(methylamino)propyl carbonate hydrochloride (1.18 temperature for 3 hrs. After concentration under reduced (0.59 g) in tetrahydrofuran was dropwise added a solution concentrated under reduced pressure, and the residue was (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was pressure, water (50 mL) was added to the residue and the cooling. After stirring under ice-cooling for 30 min., mixture was extracted with ethyl acetate (50 mL). The benzimidazole (1.10 g), triethylamine (0.83 mL) and 4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hdropwise added, and the mixture was stirred at room and dried over anhydrous magnesium sulfate.

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dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl

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acetate:hexane=1:2, then 1:1) to give the title compound (0.88 g) as a yellow amorphous solid.

'A-NMR(CDCl<sub>3</sub>): 1.29(3H,t,J=7.2Hz), 2.10-2.20(2H,m),
2.22(3H,s), 3.02(3H,bs), 3.55-3.77(2H,m), 4.14-4.30(4H,m),
4.37(2H,q,J=7.8Hz), 4.83-5.13(2H,m), 6.64(1H,d,J=5.6Hz),
7.35-7.46(3H,m), 7.82(1H,d,J=8.1Hz), 8.35(1H,d,J=5.6Hz).
Synthetic Example 43

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3-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazol-1-yl]carbonyl]amino]propyl acetate

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To a solution (40 mL) of bis(trichloromethyl) carbonate (methylamino)propyl acetate hydrochloride (1.90 g) obtained (2 mL) of pyridine (0.95 mL) in tetrahydrofuran under icecooling. After stirring under ice-cooling for 30 min., 3added, and the mixture was stirred at room temperature for (1.19 g) in tetrahydrofuran was dropwise added a solution 3 hrs. After concentration under reduced pressure, water extracted with ethyl acetate (100 mL). The ethyl acetate dimethylaminopyridine (catalytic amount) were added, and ξ layer was washed with saturated brine (100 mL) and dried riethylamine (1.68 mL) in tetrahydrofuran was dropwise (100 mJ.) was added to the residue, and the mixture was benzimidazole (1.99 g), triethylamine (1.50 mL) and 4over anhydrous magnesium sulfate. After concentration in Reference Example 42 was added.  $\Lambda$  solution (2 mL) tetrahydrofuran (40 mL). (R)-2-[[[3-Methyl-4-(2,2,2under reduced pressure, the residue was dissolved in trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lH-

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the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (1.22 g) as a yellow amorphous solid.

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.97(3H,s), 2.05-2.15(2H,m), 2.22(3H,s), 3.03(3H,bs), 3.42-3.72(2H,m), 4.10-4.22(2H,m), 4.37(2H,q,J=7.8Hz), 4.85-5.13(2H,m), 6.64(1H,d,J=5.6Hz), 7.24-7.44(3H,m), 7.83(1H,d,J=7.5Hz), 8.35(1H,d,J=5.6Hz). Synthetic Example 44

trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

3-[Methy1[[(R)-2-[[[3-methy1-4-(2,2,2-

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To a solution (20 mL) of bis(trichloromethyl) carbonate (methylamino)propane-1,2-diyl diacetate hydrochloride (1.35 (R) - 2 - [[3 - Methy] - 4 ethyl acetate layer was washed with saturated brine (50 mL) g) obtained in Reference Example 46 was added. A solution and dried over anhydrous magnesium sulfate. The layer was sthyl acetate (50 mL). The ethyl acetate layer was washed cooling. After stirring under ice-cooling for 30 min., 3-(1 mL) of pyridine (0.49 mL) in tetrahydrofuran under iceemperature for 3 hrs. After concentration under reduced (0.59 g) in tetrahydrofuran was dropwise added a solution of triethylamine (0.84 mL) in tetrahydrofuran was pressure, water (50 mL) was added to the residue and the concentrated under reduced pressure, and the residue was dimethylaminopyridine (catalytic amount) were added, and added to the residue and the mixture was extracted with pressure, the residue was purified by basic silica gel (2, 2, 2-trifluoroethoxy) -2-pyricyl]methyl]sulfinyl]-1Hwith saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced dropwise added, and the mixture was stirred at room. penzimidazole (1.27 g), triethylamine (0.96 mL) and concentration under reduced pressure, water (50 mL) mixture was extracted with ethyl acetate (50 mL). the mixture was stirred at 60°C overnight. After dissolved in tetrahydrofuran (20 mL).

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acetate:hexane=1:2, then 1:1) to give the title compound column chromatography (eluted with ethyl (C.64 g) as a yeliow amorphous solid.

4.38(2H,q,J=7.8Hz), 4.85-5.05(2H,m), 5.42-5.50(1H,m), 6.63-6.66(1H,m), 7.38-7.51(3H,m), 7.78-7.85(1H,m), 8.33-'H-NMR(CDC13): 2.05(3H,s), 2.13(3H,s), 2.23(3H,s), 3.07(3H,bs), 3.42-3.95(2H,m), 4.06-4.43(2H,m), 8.36(1H,m)

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Diethyl 3-[methyl[[(3)-2-[[[3-methyl-4-(2,2,2benzimidazol-1-yl]carbonyl]amino]propane-1,2-diyl trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbiscarbonate

Synthetic Example 45

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To a solution (20 mL) of bis(trichloromethyl) carbonate (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-(0.59 g) in tetrahydrofurar was dropwise added a solution cooling. After stirring under ice-cooling for 30 min.,

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(50 mL). The ethyl acetate layer was washed with saturated hydrochloride (1.71 g) obtained in Reference Example 47 was stirred at room temperature for 3 hrs. After concentration ethyl acetate layer was washed with saturated brine (50 mL) The layer was concentrated under reduced pressure, and the (catalytic amount) were added, and the mixture was stirred purified by basic silica gel column chromatography (eluted with ethyl acetate: hexane=1:2, then 1:1) to give the title (R)-2orine (50 mL) and dried over anhydrous magnesium sulfate. residue and the mixture was extracted with ethyl acetate pressure, water (50 mL) was added to the residue and the ij etrahydrofuran was dropwise added, and the mixture was The under reduced pressure, water (50 mL) was added to the concentration under reduced pressure, the residue was at 60°C overnight. After concentration under reduced itethyl 3-(methylamino)propane-1,2-diyl biscarbonate added. A solution (1 mL) of triethylamine (0.84 mL) pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.53 g), triethylamine (1.16 mL) and 4-dimethylaminopyridine and dried over anhydrous magnesium sulfate. After residue was dissolved in tetrahydrofuran (20 mL). mixture was extracted with ethyl acetate (50 mL). compound (1.42 g) as a yellow amorphous solid. [[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-Ŋ 10 15 20 25

'H-NMR(CDCl3): 1.28-1.34(6H,m), 2.22(3H,s), 3.07(3H,bs),

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3.42-4.60(10H,m), 4.85-5.08(2H,m), 5.30-5.42(1H,m), 6.62-6.64(1H,m), 7.37-7.42(3H,m), 7.80-7.83(1H,m), 8.32-8.35(1H,m).

Synthetic Example 46

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pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-2-[[[5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2yl]carbonyl](methyl)amino]ethyl 3-chlorobenzoate

After concentration under reduced (1 mL) of pyridine (0.162 mL) in tetrahydrofuran under ice-To a solution (7 mL) of bis(trichloromethyl) carbonate (0.194 g) in tetrahydrofuran was dropwise added a solution (methylamino)ethyl 3-chlorobenzoate hydrochloride (0.50 g) obtained in Reference Example 7 was added. A solution (1 pressure, water (15 mL) was added to the residue, and the cooling. After stirring under ice-cooling for 30 min., nL) of triethylamine (0.279 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2.5 hrs.

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ethyl acetate layer was washed with saturated brine (15 mL) imidazo[4,5-b]pyridine (0.445 g) synthesized by the method sthyl acetate (70 mL). The ethyl acetate layer was washed described in JP-A-63-146882, triethylamine (0.357 mL) and 5-Methoxy-2-[[(4added to the residue, and the mixture was extracted with acetate:hexane=1:2, then 1:1) to give the title compound concentration under reduced pressure, water (30 mL) was The pressure, the residue was purified by basic silica gel concentration under reduced pressure, the residue was and the with saturated brine (20 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1Hand dried over anhydrous magnesium sulfate. After mixture was extracted with ethyl acetate (50 mL). mixture was stirred at 60°C for 14 hrs. After 4-dimethylaminopyridine (0.012 g) were added, solumn chromatography (eluted with ethyl dissolved in tetrahydrofuran (10 mL). 10 15

6.77(1H,d,J=8.8Hz), 7.36(1H,m), 7.52(1H,m), 7.80-8.03(3H,m), 'H-NMR(CDCl<sub>3</sub>): 2.21(3H,s), 2.23(3H,s), 3.32,3.38(total H,s), 3.72(3H,s), 3.81(3H,s), 3.92-4.09(2H,m), 4.50-1.73(2H,m), 4.87(1H,d,J=13.4Hz), 4.94(1H,d,J=13.4Hz), (0.360 g) as a colorless amorphous solid. 8.20(1H,s).

Synthetic Example 47

2-[Methy1[[2-[[[3-methy1-4-(2,2,2-trifluoroethoxy]-2-Pyridyl]methyl]sulfinyl[-1H-benzimidazol-1yl]carbonyl]amino]ethyl acetate

To a solution (20 mL) of bis(trichloromethyl) carbonate (methylamino) ethyl acetate hydrochloride (0.922 g) obtained (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-(0.582 g) in tetrahydrofuran was dropwise added a solution added, and the mixture was stirred at room temperature for cooling. After stirring under ice-cooling for 1 hr., 2extracted with ethyl acetate (80 mL). The ethyl acetate triethylamine (0.84 mL) in tetrahydrofuran was dropwise A solution (1 mL) of layer was washed with saturated brine (25 mL) and dried over anhydrous magnesium sulfate. After concentration 2.5 hrs. After concentration under reduced pressure, (40 ml) was added to the residue, and the mixture was under reduced pressure, the residue was dissolved in tetrahydrofuran (15 mL). 2-[[[3-Methyl-4-(2,2,2in Reference Example 2 was added.

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dimethylaminopyridine (0.036 g) were added, and the mixture The ethyl acetate layer was washed with saturated brine (30 was stirred at 60°C for 4.5 hrs. After concentration under purified by silica gel column chromatography (eluted with reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). H-NWR(CDCl<sub>3</sub>): 2.10(3H,s), 2.24(3H,s), 3.09(3H,bs), 3.60mL) and dried over anhydrous magnesium sulfate. After sthyl acetate:hexane=1:1, then 2:1) to give the title concentration under reduced pressure, the residue was benzimidazole (1.10 g), triethylamine (0.84 mL) and trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-1Hcompound (1.18 g) as a colorless solid. 10

4.00(2H,br), 4.25-4.50(2H,m), 4.38(2H, q,J=7.8Hz), 4.84-

5.18(2H,m), 6.64(1H,d,J=5.6Hz), 7.36-7.48(3H,m), 7.85(1H, d, J=7.8Hz), 8.35(1H, d, J=5.6Hz).

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Synthetic Example 48

Ethyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

benzimidazol-1-yl]carbonyl]amino]ethyl carbonate

A solution of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (130 g), triethylamine (63.8 mL), 4-dimethylaminopyridine (0.86 g) and 2-

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[(chlorocarbonyl) (methyl) amino]ethyl ethyl carbonate (84.8 g) obtained in Reference Example 34 in tetrahydrofuran (813 mL) was stirred at 45-50°C for 18 hrs. The reaction mixture was concentrated under reduced pressure and water (300 mL) was added to the residue, and the mixture was extracted with ethyl acetate (700 mL). The ethyl acetate layer was washed 3 times with saturated brine (300 mL), and anhydrous magnesium sulfate (130 g) and activated carbon (13 g) were added. The mixture was stirred at room temperature for 30 min. and filtrated. The filtrate was concentrated under reduced pressure and the residue was dissolved in diethyl ether (600 mL) containing

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under reduced pressure. This step was further repeated twice. The obtained oily substance was dissolved in ethanol (200 mL) containing triethylamine (2.45 mL) and water (120 mL) was dropwise added under ice-cooling. The precipitated crystals were collected by filtration, washed 3 times with ice-cooled ethanol-water (volume ratio 1:1, 150 mL) and dried to give the title compound (172.2 g) as colorless solid. The NMR(CDCl<sub>3</sub>) showed the same chart as with the compound obtained in Synthetic Example 14.

2-Ethoxyethyl 2-[methyl[[(R]-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate

Synthetic Example 49

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To a solution (20 mL) of bis(trichloromethyl)carbonate (0.43 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.35 mL) in tetrahydrofuran under ice-

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triethylamine (0.49 mL), and the mixture was concentrated

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cooling. After stirring under ice-cooling for 10 min., 2-ethoxyethyl 2-(methylamino)ethyl carbonate hydrochloride (0.82 g) obtained in Reference Example 48 was added. A solution (1 mL) of triethylamine (0.60 mL) in

stirred at room temperature for 3 days. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over annydrous magneslum sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-

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pyridyl]methyl]sulfinyl]-liH-benzimidazole (1.11 g), triethylamine (0.63 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60°C for 6 hrs. and at room temperature for 11 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel

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acetate:hexane=3:7, then ethyl acetate:hexane=7:3) to give the title compound (1.39 g) as a yellow amorphous solid.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.19(3H,t,J=6.9Hz), 2.23(3H,s), 3.09(3H,bs),

5 4.27-4.34(2H,m), 4.39(2H,q,J=7.8Hz), 4.47(2H,m), 4.80-

3.40-4.20(2H,br), 3.53(2H,q,J=6.9Hz), 3.63-3.69(2H,m),

5.20(2H,m), 6.65(1H,d,~=5.6Hz), 7.30-7.52(3H,m),

7.84(1H,d,J=7.5Hz), 8.35(1H,d,J=5.6Hz).

Synthetic Example 50

3-Methoxypropyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazol-1-yl]carbonyl]amino]ethyl carbonate

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Methyl-4-(2,2,2-trifluoroethoxy)-2-

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To a solution (20 mL) of bis(trichloromethyl) carbonate (0.53 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.44 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 5 min., 3-methoxypropyl 2-(methylamino)ethyl carbonate hydrochloride

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column chromatography (eluted with ethyl

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dimethylaminopyridine (0.037 g) were added, and the mixture dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4stirred at room temperature for 1 hr. After concentration Crystallization from diethyl ether gave the title compound was stirred at 60°C for 6 hrs. and at room temperature for nydrochloric acid (20 mL) and saturated brine (50 mL) and 6 hrs. After concentration under reduced pressure, water under reduced pressure, the residue was purified by basic residue and the mixture was extracted with ethyl acetate concentrated under reduced pressure, and the residue was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried under reduced pressure, water (50 mL) was added to the dried over anhydrous magnesium sulfate. The layer was tetrahydrofuran was dropwise added and the mixture was (50 mL). The ethyl acetate layer was washed with 0.2N (2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hbenzimidazole (1.11 g), triethylamine (0.63 mL) and 4over anhydrous magnesium sulfate. After concentration (0.82 g) obtained in Reference Example 49 was added. (50 mL) was added to the residue and the mixture was silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate:hexane=7:3). solution (1 mL) of triethylamine (0.75 mL) in (0.70 g) as a colorless solid.

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H-NMR(CDCl<sub>3</sub>): 1.94(2H, quintet, J=6.2Hz), 2.23(3H, s),

3.09(3H,bs), 3.31(3H,s), 3.40-4.20(2H,br),

3.44(2H,t,J=6.2Hz), 4.25(2H,t,J=6.5Hz), 4.38(2H,q,J=7.8Hz),

4.44(2H,m), 4.80-5.20(2H,m), 6.64(1H,d,J=5.6Hz), 7.35-

5 7.48(3H,m), 7.83(1H,d,J=7.8Hz), 8.34(1H,d,J=5.6Hz).

Synthetic Example 51

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

>>enzimidazol-1-yl]carbonyl]amino]ethyl N,N-

dimethylglycinate

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2-(Methylamino)ethyl N.N-dimethylglycinate dihydrochloride (1.06 g) obtained in Reference Example 50 was added to tetrahydrofuran (40 mL) and the mixture was stirred for a while, to which bis(trichloromethyl)carbonate (0.77 g) was added. After ice-cooling, a solution (5 mL) of triethylamine (2.17 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 3

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methanol:ethyl acetate=1:19). Crystallization from diethyl dimethylaminopyridine (0.037 g) were added, and the mixture (50 ml). The ethyl acetate layer was washed with saturated After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted The mixture was washed with an mL) and saturated brine (50 mL×2) and dried over anhydrous and at room temperature for residue, and the mixture was extracted with ethyl acetate ice-cooled aqueous sodium hydrogen carbonate solution (50 3 days. 4-Dimethylaminopyridine (0.037 g) was added, and the mixture was further stirred at 60°C for 6 hrs. After brine (50 mL) and dried over anhydrous magnesium sulfate. concentration under reduced pressure, an aqueous socium with ethyl acetate:hexane=1:1, then ethyl acetate, then hrs. The precipitated solid was filtered off and ethyl benzimidazole (1.11 g), triethylamine (0.63 mL) and 4ether gave the title compound (0.41 g) as a colorless (R) -2-[[[3-Methyl-4-(2,2,2magnesium sulfate. The layer was concentrated under hydrogen carbonate solution (50 mL) was added to the reduced pressure, and the residue was dissolved in trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1Hwas stirred at 60°C for 6 hrs. acetate (80 mL) was added. tetrahydrofuran (20 mL). solid.

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 $^{1}$ H-NMR(CDCl<sub>3</sub>): 2.23(3H,s), 2.35(6H,s), 3.08(3H,bs),

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3.21(2H,s), 3.50-4.20(2H,br), 4.38(2H,q,J=7.8Hz),

4.44(2H,m), 4.80-5.18(2H,m), 6.64(1H,d,J=5.6Hz), 7.36-

7.48(3H,m), 7.84(1H,d,J=6.9Hz), 8.35(1H,d,J=5.6Hz).

Synthetic Example 52

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S-[2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-IHbenzimidazol-1-yl]carbonyl]amino]ethyl] thioacetate

S-[2-(Methylamino)ethyl] thioacetate hydrochloride (0.75 g) obtained in Reference Example 51 was added to tetrahydrofuran (30 mL) and the mixture was stirred for a while, to which bis(trichloromethyl)carbonate (0.66 g) was added. After ice-cooling, a solution (10 mL) of triethylamine (1.85 mL) in tetrahydrofuran was dropwise added and the mixture was stirred under ice-cooling for 30 min. and at room temperature for 30 min. The precipitated solid was filtered off and ethyl acetate (50 mL) was added to the filtrate. The mixture was washed with ice-cooled 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL)

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dimethylaminopyridine (0.032 g) were added, and the mixture (R)-2-[[[3-Methyl-4and dried over anhydrous magnesium sulfate. The layer was under reduced pressure, the residue was purified by silica was stirred at 60°C for 6 hrs. and at room temperature for gel column chromatography (eluted with acetone:hexane=3:7, then acetone:hexane=7:3) to give the title compound (1.19 8 hrs. After concentration under reduced pressure, water concentrated under reduced pressure, and the residue was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried benzimidazole (0.96 g), triethylamine (0.54 mL) and 4-After concentration (2, 2, 2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl}-1H-(50 mL) was added to the residue and the mixture was dissolved in tetrahydrofuran (20 mL). over anhydrous magnesium sulfate. as a yellow amorphous solid.

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7.83(1H, d, J=6.9Hz), 8.35(1H, d, J=5.7Hz) Synthetic Example 53 20

3.22(2H,t,J=6.6Hz), 3.67(2H,m), 4.38(2H,q,J=7.8Hz), 4.80-

5.20(2H,m), 6.64(1H,d,J=5.7Hz), 7.35-7.50(3H,m),

H-NMR(CDC13): 2.23(3H,s), 2.34(3E,s), 3.10(3H,bs),

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benzimidazol-1-yl]carbonyl]amino]ethoxy]ethyl carbonate Ethyl 2-[2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2trifluoroethoxy) -2-pyridyl]methyl]sulfiny:]-1H-

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To a solution (40 mL) of bis(trichloromethyl)carbonate lydrochloride (2.73 g) obtained in Reference Example 52 was stirred at room temperature for 3 hrs. After concentration saturated brine (100 mL) and dried over annydrous magnesium (2 mL) of pyridine (0.95 mL) in tetrahydrofuran under ice-(1.19 g) in tetrahydrofuran was dropwise added a solution residue, and the mixture was extracted with ethyl acetate sulfate. After concentration under reduced pressure, the tetrahydrofuran was dropwise added, and the mixture was inder reduced pressure, water (100 mL) was added to the cooling. After stirring under ice-cooling for 30 min., added. A solution (2 mL) of triethylamine (1.68 mL) (100 mL). The ethyl acetate layer was washed with ethyl 2-[2-(methylamino)ethoxy]ethyl carbonate

residue was dissolved in tetrahydrofuran (40 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifl:oxoethoxy]-2-

pyridyl]methyl]sulfinyl]-1:i-benzimidazole (2.80 g),
triethylamine (2.11 mL) and 4-dimethylaminopyridine

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(catalytic amount) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compounc (2.19 g) as a yellow amorphous solid.

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<sup>1</sup>H-NWR(CDCL<sub>3</sub>): 1.28(3H,t,J=7.2Hz), 2.24(3H,s), 3.10(3H,bs), 3.38-3.80(6H,m), 4.18(2H,q,J=7.2Hz), 4.27-4.34(2H,m), 4.38(2H,q,J=8.4Ez), 4.83-5.30(2H,m), 6.65(1H,d,J=5.7Hz), 7.35-7.50(3H,m), 7.84(1H,d,J=7.8Hz), 8.36(1H,d,J=5.7Hz). Synthetic Example 54

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Ethyl 2-[methyl[[2-[methyl[[(R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lHbenzimidazol-1-

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yl]carbonyl]amino]ethoxy]carbonyl]amino]ethyl carbonate

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No. H. S. H.

To a solution (20 mL) of bis(trichloromethyl) carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under icecoling. After stirring under ice-cooling for 30 min., ethy: 2-[methyl[[2-(methylamino)ethoxy]carbonyl]amino]ethyl carbonate hydrochloride (1.71 g) obtained in Reference Example 53 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed

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with saturated brine (50 mL) and dried over anhydrous The layer was concentrated under magnesium sulfate.

reduced pressure, and the residue was dissolved in

tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-

trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

S

benzimidazole (1.59 g), triethylamine (1.20 mL) and 4-

dimethylaminopyridine (catalytic amount) were added, and

the mixture was stirred at 60°C overnight. After

concentration under reduced pressure, water (50 mL) was

added to the residue and the mixture was extracted with

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ethyl acetate (50 mL). The ethyl acetate layer was washed

with saturated brine (50 mL) and dried over anhydrous

magnesium sulfate. After concentration under recuced

gel pressure, the residue was purified by basic silica

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acetate:hexane=1:2, then 1:1) to give the title compound column chromatography (eluted with ethyl

"H-NMR(CDCl3): 1.24-1.31(3H,m), 2.24(3H,bs), 2.97-

(1.62 g) as a yellow amorphous solic.

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2.99(3H,m), 3.10(3H,bs), 3.55-3.58(2H,m), 4.09-4.50(10H,m)

4.88-5.08(2H,m), 6.65(1H, t, J=5.7Hz), 7.36-7.48(3H,m), 20

7.85(1H, d, J=6.9Hz), 8.36(1H, d, J=5.7Hz).

Synthetic Example 55

Ethyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-

pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-

yl]carbonyl](methyl)amino]ethyl carbonate

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To a solution (10 mL) of bis(trichloromethyl) carbonate (1 mL) of pyridine (0.243 mL) in tetrahydrofuran under icecooling. After stirring under ice-cooling for 1 hr., ethyl (0.291 g) in tetrahydrofuran was dropwise added a solution A solution (1 ML) of triethylamine (0.418 mL) in tetrahydrofuran was 2- (methylamino) ethyl carbonate hydrochloride (0.551 dropwise added, and the mixture was stirred at room obtained in Reference Example 14 was added.

sthyl acetate layer was washed with saturated brine (15 mL) temperature for 2 hrs., After concentration under reduced pressure, water (15 mL) was added to the residue, and the nixture was extracted with ethyl acetate (50 mL). and dried over anhydrous magnesium sulfate. After

5-Methoxy-2-[[[(4concentration under reduced pressure, the residue was nethoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-lHdissolved in tetrahydrofuran (10 mL).

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benzimidazole (0.817 g), triethylamine (0.661 mL) and 4-dimethylaminopyridine (0.312 g) were added, and the mixture was stirred at 60°C for 12 hrs. After concentration under reduced pressure, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give a 3:2 mixture (0.92 g) of the title compound and ethyl 2-[[[6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-

S

yl]carbonyl](methyl)aminolethyl carbonate as a pale-yellow amorphous solid.

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pyridyl)methyl]sulfinyl;-1H~benzimidazol-1-

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.27-1.34(3H,m), 2.10-2.30(3H,m), 2.23(3H,s), 2.99-3.23(3H,m), 3.40-3.85(2H,m), 3.69(6/5H,s),

3.71(9/5H,s), 3.86(6/5H,s), 3.88(9/5H,s), 4.14-4.25(2H,m), 4.38-4.60(2H,m), 4.82-5.06(2H,m), 6.92-7.08(7/5H,m),

20 7.33(3/5H,d,J=9.0Hz), 7.66(1H,m), 8.21(1H,s).

Synthetic Example 56

2-[[[5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl)methyl]sulfinyl]-IH-benzimidazol-1yl]carboryl](phenyl)amino]ethyl acetate

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SCOCH<sub>3</sub> COCH<sub>3</sub>

dimethyl-2-pyr1dyl)methyl]sulfinyl]-1H-benzimidazole (0.829 To a solution (10 mL) of bis(trichloromethyl) carbonate (1 mī) of pyridine (0.243 mL) in tetrahydrofuran under ice-(0.291 g) in tetrahydrofuran was dropwise added a solution cooling. After stirring under ice-cooling for 30 min., 2-. added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water Inilinoethyl acetate hydrochloride (0.647 g) obtained in triethylamine (0.419 mL) in tetrahydrofuran was dropwise extracted with ethyl acetate (50 mL). The ethyl acetate g), triethylamine (0.669 mL) and 4-dimethylaminopyridine tetrahydrofuran (10 mL). 5-Methoxy-2-[[(4-methoxy-3,5over anhydrous magnesium sulfate. After concentration mL) was added to the residue, and the mixture was Reference Example 27 was added. A solution (1 mL) of under reduced pressure, the residue was dissolved in and layer was washed with saturated brine (15 mL)

for 14 hrs. After concentration under reduced pressure,
for 14 hrs. After concentration under reduced pressure,
water (40 mL) was added to the residue, and the mixture was
extracted with ethyl acetate (80 mL). The ethyl acetate
layer was washed with saturated brine (15 mL) and dried
over anhydrous magnesium sulfate. After concentration
under reduced pressure, the residue was purified by basic
silica gel column chromatography (eluted with ethyl
acetate:hexane=1:2) to give a 1:1 mixture (1.10 g) of the
title compound and 2-[[[6-methoxy-2-[[(4-methoxy-3,5dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazcl-1yl]carbonyl](phenyl)amino]ethyl acetate as a colorless
amorphous solid.

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>): 1.99(3H,s), 2.19(1.5E.s), 2.21(1.5H,s), 2.25(3H,s), 3.70(1.5H,s), 3.71(3H,s), 3.78(1.5H,s), 3.84(1.5H,s), 4.15-4.56(4H,m), 4.74-4.80(1H,m), 4.91-4.98(1H,m), 6.83-6.91(1.5H,m), 7.34-7.19(3.5H,m), 7.25-7.53(2.5H,m), 7.51(0.5H,d,J=8.7Hz), 8.25(1H,s). Synthetic Example 57

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Ethyl 2-[[[(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-lH-benzimidazol-1yl]carbonyl](methyl)amino]ethyl carbonate

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HOO OOH

To a solution (10 mL) of (3)-5-methoxy-2-[[(4-methoxytriethylamine (1.08 mL) and 4-dimethylaminopyridine (0.010 ethyl acetate (50 mL). The ethyl acetate layer was washed (1.34 g) synthesized by the method described in Synthetic g), and the mixture was stirred at 60°C for 6 hrs. After 3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole Example 1 of Japanese Patent Application under PCT laidadded to the residue and the mixture was extracted with open under kohyo No. 10-504290 in tetrahydrofuran were pressure, the residue was purified by basic silica gel with saturated brine (15 mJ) and dried over anhydrous magnesium sulfate. After concentration under reduced carbonate (0.9 mL) obtained in Reference Example 34, concentration under reduced pressure, water (30 mL) added 2-[(chlorocarbonyl) (methyl) amino]ethyl ethyl column chromatography (eluted with ethyl

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acetate:hexane=1:2, then 1:1) to give a 3:2 mixture (0.92

g) of the title compound and ethyl 2-[[[(S)-6-methoxy-2-

[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-

benzimidazol-1-yl]carbonyl](methyl)amino]ethyl carbonate as

a pale-yellow amorphous solid.

'H-NMR(CDCl<sub>3</sub>): 1.25-1.34(3H,m), 2.10-2.30(3H,m),

2.23(3H,s), 2.99-3.23(3H,m), 3.40-3.85(2H,m), 3.69(6/5H,s),

3.71(9/5H,s), 3.86(6/5H,s), 3.88(9/5H,s), 4.14-4.25(2H,m),

4.38-4.60(2H,m), 4.79-5.05(2H,m), 6.92-7.08(7/5H,m),

10 7.33(3/5H, d, J=9.3Hz), 7.65(1H,n), 8.21(1H,s).

Synthetic Example 58

Ethyl 2-[[[2-[[[4-(3-methoxypropoxy)-3-methyl-2-

pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-

yl]carbonyl](methyl)amino]ethyl carbonate

To a solution (10 mL) of bis(trichloromethyl)carbonate (0.291 g) in tetrahydrofuran was dropwise added a solution

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(1 mL) of pyridine (0.243 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 2-(methylamino)ethyl carbonate hydrochloride (0.551

g) obtained in Reference Example 14 was added. A solution (1 mL) of triethylamine (0.418 mL) in tetrahydrofuran was

dropwise added, and the mixture was stirred at room

temperature for 2.5 hrs. After concentration under reduced, pressure, water (15 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The

10 ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After

concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 2-[[4-(3-

Methoxypropoxy) -3-methy1-2-pyridyl]methy1]sulfinyl]-1H-

benzimidazole (0.723 g), triethylamine (0.528 mL) and 4dimethylaminopyridine (0.012 g) were added, and the mixture

was stirred at 60°C for 17 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue,

and the mixture was extracted with ethyl acetate (80 mL).  $$^{20}$$  The ethyl acetate layer was washed with saturated brine (15  $\,$ 

mL) and dried over anhydrous magnesium sulfate. After

concentration under reduced pressure, the residue was

purified by basic silica gel column chromatography (eluted
with ethyl acetate:hexane=1:2), then by silica gel column

25 chromatography (eluted with ethyl acetate:hexane=1:1, then

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ethyl acetate) to give the title compound (0.44 g) as a colorless amorphous solid "H-NMR(CDCl<sub>3</sub>): 1.31(3H,t,J=7.1Hz), 2.05(2H,m), 2.18(3H,s), 4.01(2H,m), 4.08(2H,t,J=6.3Hz), 4.21(2H,t,J=7.1Hz), 4.38-1.54(2H,m), 4.81-5.12(2H,m), 6.68(1H,d,J=5.6Hz), 7.34-7.48(3H,m), 7.83(1H,d,J=7.8Hz), 8.27(1H,d,J=5.6Hz). 3.08(3H,bs), 3.34(3H,s), 3.54(2H,t,J=6.1Hz), 3.61-Synthetic Example 59

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2-[[[2-[[[4-(3-Methoxypropoxy)-3-methyl-2pýridyl]methyl]sulfinyl]-1H-benzimidazol-1yl]carbonyl](phenyl)amino]ethyl acetate

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To a solution (10 mL) of bis(trichloromethyl) carbonate (1 mL) of pyridine (0.243 mL) in tetrahydrofuran under ice-(0.291 g) in tetrahydrofuran was dropwise added a solution cooling. After stirring under ice-cooling for 30 min., 2unilinoethyl acetate hydrochloride (0.647 g) obtained in triethylamine (0.419 mL) in tetrahydrofuran was dropwise φ A solution (1 mL) Reference Example 27 was added.

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added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water extracted with ethyl acetate (50 mL). The ethyl acetate (20 mL) was added to the residue, and the mixture was

- water (40 mL) was added to the residue, and the mixture was nethy1-2-pyridyl]methyl]sulfinyl]-lH-benzimidazole (0.877 .0.012 g) were added, and the mixture was stirred at 60°C g), triethylamine (0.641 mL) and 4-dimethylaminopyridine for 16 hrs. After concentration under reduced pressure, layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration 2-[[[4-(3-Methoxypropoxy)-3under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). Ŋ 10
  - under reduced pressure, the residue was purified by basic extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried After concentration silica gei column chromatography (eluted with ethyl acetate:hexane=1:2), then by silica gel column over anhydrous magnesium sulfate.
- 3.35(3H,s), 3.54(2H,t,J=6.2Hz), 4.09(2H,t,J=6.2Hz), 4.14title compound (0.93 g) as a colorless amorphous solid. chromatography (eluted with ethyl acetate) to give the 4.40(4H,m), 4.80(1H,d,J=13.7Hz), 5.00(1H,d,J=13.7Hz), H-NMR(CDCl<sub>3</sub>): 1.99(3H,s), 2.07(3H.s), 2.19(3H,s),

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6.71(1H,d,J=5.7Hz), 7.03-7.34(7H,m), 7.38(1H,m), 25

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7.65(1H,m), 8.32(1H,d,J=5.7Hz) Synthetic Example 60 2-[[[5-(Difluoromethoxy)~2-[[(3,4-dimethoxy-2pyridy])methyl]sulfinyl]-lH-benzimidazol-1yl]carbonyl](methyl)amino]ethyl ethyl carbonate

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To a solution (8 mL) of bis(trichioromethyl) carbonate (0.174 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.146 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., ethyl 2-(methylamino) ethyl carbonate hydrochloride (0.330 g) obtained in Reference Example 14 was added. A solution (1 mL) of triethylamine (0.250 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate (30 mL). The

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ethyl acetate layer was washed with saturated brine (10 mL) and dried over anhydrous magnesium sulfate. After

concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (8 mL). 5-(Difluoromethoxy)-

2-[[(3,4-dimethoxy-2-pyridy])methyl]sulfinyl]-1:i-benzimidazole (0.432 g), triethylamine (0.279 mL) and 4-dimethylaminopyridine (0.008 g) were added, and the mixture was stirred at 60°C for 17.5 hrs. After concentration under reduced pressure, water (20 mL) was added to the

residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (10 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted

with ethyl acetate:hexane=1:2, then 1:1), then by silica gel column chromatography (eluted with ethyl

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acetate:hexane=2:1, then ethyl acetate) to give a 1:1 mixture (0.09 g) of the title compound and 2-[[[6-

20 pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-

(difluoromethoxy)-2-[[(3,4-dimethoxy-2-

yl]carbonyl]methylamino]ethyl ethyl carbonate as a paleyellow amorphous solid.

<sup>1</sup>H-NWR (CDCl<sub>3</sub>): 1.31(3H,t,J=7.2Hz), 3.06(3H,s), 3.42-

3.98(2H,m), 3.87(3H,s), 3.90(3H,s), 4.21(2H,q,J=7.2Hz),

25 4.36-4.54(2H,m), 4.90(1H,d,J=13.2Hz), 4.98(1H,d,J=13.2Hz),

6.54(0.5H,t,J=73.5Hz), 6.61(0.5H,t,J=73.5Hz),

6.78(13,d,J=5.3Hz), 7.15-7.25(1.5H,m),

7.44(0.5H, d, J=9.0Hz), 7.59(0.5H,s), 7.80(0.5H,d, J=9.0Hz),

8.17(1H, d, J=5.3Hz).

Synthetic Example 61

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2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-

trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-

benzimidazol-1-yl]carbonyl]amino]ethyl 1-methylpiperidine-4-carboxylate

stirred for a while, to which bis(trichloromethyl)carbonate 2-(Methylamino)ethyl 1-methylpiperidine-4-carboxylate of triethylamine (2.01 mL) in tetrahydrofuran was dropwise (0.53 g) was added. After ice-cooling, a solution (50 mL) obtained in Reference Example 54 was added to tetrahydrofuran (50 mL) and the mixture was dihydrochloride (0.98 g)

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2.24-2.38(1H,m), 2.75-2.85(2H,m), 3.07(3H,bs), 3.40-

4.10(2H,br), 4.38(2H,q,J=7.8Hz), 4.40(2H,m), 4.80-5.10(2H,br), 6.64(1H,d,J=5.6Hz), 7.36-7.47(3H,m),

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dimethylaminopyridine (0.049 g) were added, and the mixture solution (50 mL) was added to the residue, and the mixture purified by basic silica gel column chromatography (eluted acetate layer was washed with saturated brine (50 mL) and added and the mixture was stirred at room temperature for Ethyl acetate (100 mL) was added and the mixture was washed with an aqueous sodium hydrogen carbonate solution was stirred at 60°C overnight. After concentration under anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in with ethyl acetate:hexane=7:3, then ethyl acetate, then methanol:ethyl acetate=1:19) to give the title compound cenzimidazole (0.74 g), triethylamine (0.56 mL) and 4reduced pressure, an aqueous sodium hydrogen carbonate H-NMR(CDCl3): 1.65-2.05(6H,m), 2.23(3H,s), 2.25(3H,s), concentration under reduced pressure, the residue was (R) -2-[[[3-Methy1-4-(2,2,2was extracted with ethyl acetate (50 mL). The ethyl (100 mL) and saturated brine (80 mL) and dried over trifluoroethoxy>-2-pyridyl]methyl]sulfinyl]-1Hdried over anhydrous magnesium sulfate. After (0.78 g) as a yellow-green amorphous solid. tetrahydrofuran (20 mL). 20 9 15 S

7.84(1H, d, J=7.8Hz), 8.35(1H, d, J=5.6Hz).

Synthetic Example 62

2-[[4-(Aminocarbonyl)phenyl][[(R)-2-[[[3-methyl-4-(2, 2, 2-trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-1Hbenzimidazol-1-yl]carbonyl]amino]ethyl acetate

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To a solution (20 mL) of bis(trichloromethyl) carbonate with 0.2N hydrochloric acid (20 mL) and saturated brine (50 (0.67 g) obtained in Reference Example 55 and triethylamine (10 mL) of 2-[[4-(aminocarbonyl)phenyl]amino]ethyl acetate ethyl acetate (50 mL). The ethyl acetate layer was washed (0.45 g) in tetrahydrofuran was dropwise added a solution After (3.63 mL) in tetrahydrofuran under ice-cooling, and the concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with After concentration under reduced pressure, the residue was mixture was stirred at room temperature for 1 hr. mL) and dried over anhydrous magnesium sulfate.

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iimethylaminopyridine (0.037 g) were added, and the mixture dissolved in tetrahydrofuran (30 mL). (R)-2-[[[3-Methyl-4ethyl acetate (50 mL). The ethyl acetate layer was washed overnight. After concentration under reduced pressure, an added to the residue, and the mixture was extracted with was stirred at 60°C for 30 min. and at room temperature agueous sodium hydrogen carbonate solution (50 mL) was benzimidazole (1.11 g), triethylamine (0.63 mL) and 4-(2, 2, 2-trifluoroethoxy) -2-pyridyl]methyl]sulfinyl]-1H-2

pressure, the residue was purified by basić silica gel After concentration under reduced with saturated brine (50 mL) and dried over anhydrous column chromatography (eluted with ethyl magnesium sulfate.

acetate:hexane=4:6, then 6:4, then 8:2) to give the title |.41(2H,q,J=7.9Hz), 4.80-5.20(2H,br), 6.69(1H,d,J=5.7Hz), 7.26-7.38(3H,m), 7.48(2H,d,J=8.9Hz), 7.54(2H,d,J=8.9Hz),  $H-NMR(CDCl_3)$ : 1.99(3H,s), 2.26(3H,s), 4.15-4.55(4H,m), compound (1.26 g) as a yellow amorphous solid. 7.66-7.73(1H,m), 8.39(1H,d,J=5.7Hz)

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Synthetic Example 63 20

oenzimidazol-1-yl}carbonyl]amino]ethyl 1-methyl-4trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-2-[Methy1[[(R)-2-[[[3-methy1-4-(2,2,2piperidinyl carbonate 307

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2-(Methylamino)ethyl 1-methyl-4-piperidinyl carbonate of triethylamine temperature for 1 hr., the precipitated solid was filtered acetate (50 mL) was added, and the mixture was washed with dihydrochloride (1.01 g) obtained in Reference Example 56 was added to tetrahydrofuran (30 mL) and, after stirring an ice-cooled aqueous sodium hydrogen carbonate solution anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in for a while, ice-cooled. Bis(trichloromethyl)carbonate After off. After concentration under reduced pressure, ethyl tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-(50 mL) and saturated brine (50 mL), and dried over (1.95 mL) in tetrahydrofuran was dropwise added. stirring under ice-cooling for 1 hr. and at room (0.69 g) was added and a solution (10 mL)

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trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.63 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60°C overnight. After concentration under

- reduced pressure, an aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After
- concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate, then methanol:ethyl acetate=1:19) to give the title compound (0.70 g) as a yellow amorphous solid.
- 15 <sup>1</sup>F-NMR(CDCl<sub>3</sub>): 1.70-1.86(2H,m), 1.90-2.04(2H,m), 2.23(3H,s), 2.28(3H,s), 2.10-2.35(2H,m), 2.60-2.72(2H,m), 3.08(3H,bs), 3.40-4.20(2H,br), 4.39(2H,q,J=7.9Hz),
- 4.44(2H,m), 4.60-4.74(1H,m), 4.80-5.15(2H,br), 6.65(1H,d,J=5.9Hz), 7.35-7.52(3H,m), 7.84(1H,d,J=7.5Hz), 8.35(1H,d,J=5.9Hz).

2-[[4-(Aminocarbonyl)phenyl][[2-[[[3-methyl-4-(2,2,2-rifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-lH-benzimidazol-1-yl]carbonyl]amino]ethyl acetate

Synthetic Example 64

(0.22 g) obtained in Reference Example 55 and triethylamine (20 mL) was added, and the mixture was extracted with ethyl To a solution (5 mL) of bis(trichloromethyl)carbonate mixture was stirred at room temperature for 30 min. Water saturated brine (20 mL) and dried over anhydrous magnesium (5 mL) of 2-[[4-(aminocarbonyl)phenyl]amino]ethyl acetate residue was dissolved in tetrahydrofuran (10 mL). 2-[[[3-(0.12 g) in tetrahydrofuran was dropwise added a solution acetate (30 mL). The ethyl acetate layer was washed with sulfate. After concentration under reduced pressure, the (0.17 mL) in tetrahydrofuran under ice-cocling, and the Methyl-4-(2,2,2-trifluoroethoxy)-2-

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hr. After concentration under reduced pressure, an aqueous sodium hydrogen carbonate solution (20 mL) was added to the triethylamine (0.28 mL) and 4-dimethylaminopyridine (0.012 g) were added, and the mixture was stirred at 60°C for

pyridyl]methyl]sulfinyl]-lH-benzimidazole (0.37 g),

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The ethyl acetate layer was washed with saturated After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted then 8:2) to give residue, and the mixture was extracted with ethyl acetate brine (20 mL) and dried over anhydrous magnesium sulfate. the title compound (0.34 g) as a pale-yellow amorphous with ethyl acetate:hexane=3:7, then 5:5, (30 mL).

'H-NMR(CDCl<sub>3</sub>): 1.99(3H,s), 2.26(3H,s), 4.15-4.55(4H,m),

4.41(2H,q,J=7.9Hz), 4.80-5.20(2H,br), 6.69(1H,d,J=5.9Hz), 7.26-7.40(3H,m), 7.47(2H,d,J=8.8Hz), 7.54(2H,d,J=8.8Hz), 7.65-7.74(1H,m), 8.38(1H,d,J=5.9Hz). 10

Synthetic Example 65

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(-)-Ethyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3yl]carbonyl] (methyl) amino]ethyl carbonate

5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-

resolution to give a (-) enantiomeric form (0.10 g) thereof sodium sulfate. After concentration under reduced pressure, triethylamine (0.080 mL) and 4-dimethylaminopyridine (0.007 ethyl acetate (50 mL). The ethyl acetate layer was washed synthesized according to the method described in JP-A-63-To a solution (5 mJ) of this form in tetrahydrofuran were g) and the mixture was stirred at 50°C for 18 hrs. After chromatography (eluted with ethyl acetate:hexane=2:1) to concentration under reduced pressure, water (30 mL) was added to the residue and the mixture was extracted with with saturated brine (30 mL) and dried over anhydrous carbonate (0.081 g) obtained in Reference Example 34, give the title compound (0.053 g) as a colorless oil. 146882 was subjected to preparative HPLC for optical the residue was purified by basic silica gel column 3.15,3.32(total 3H,s), 3.73(3H,s), 3.90-4.55(9H,m), pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine added 2-[(chlorocarbonyl)(methyl)amino]ethyl ethyl 6.80(1H, d, J=8.8Hz), 7.96(1H, d, J=8.8Hz), 8.23(1H, s) H-NMR(CDCl<sub>3</sub>): 1.30(3H,t,J=7.1Hz), 2.24(6H,s), 4.85(1H,d,J=13.2Hz), 4.97(1H,d,J=13.2Hz), Synthetic Example 66

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(+)-Ethyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3yl]carbonyl](methyl)amino]ethyl carbonate

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chromatography (eluted with ethyl acetate:hexane=2:1) to

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resolution to give a (+) enantiomeric form (0.10 g) thereof. sodium sulfate. After concentration under reduced pressure, triethylamine (0.080 mL) and 4-dimethylaminopyridine (0.007 sthyl acetate (50 mL). The ethyl acetate layer was washed synthesized according to the method described in JP-A-63a solution (5 mL) of this form in tetrahydrofuran were g) and the mixture was stirred at 50°C for 18 hrs. After added to the residue and the mixture was extracted with with saturated brine (30 mL) and dried over anhydrous carbonate (0.081 g) obtained in Reference Example 34, 146882 was subjected to preparative HPLC for optical concentration under reduced pressure, water (30 mL) the residue was purified by basic silica gel column pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine added 2-[(chlorocarbonyl)(methyl)amino]ethyl ethyl 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-

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granules of  $710^{
m µm-1400^{
m µm}}$ .

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give a 2:1 mixture (0.115 g) of the title compound and (+)ethyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridin-1yl]carbonyl](methyl)amino]ethyl carbonate as a colorless

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'H-NNR(CDCl<sub>3</sub>): 1.20-1.38(3H,m), 2.24(6H,s),
3.08,3.15,3.33(total 3H,s), 3.73(3H,s), 3.88-4.55(9H,m),
4.78-5.05(2H,m), 6.80,6.86(1H,d,J=8.8Hz),
7.76,7.96(1H,d,J=8.8Hz), 8.21,8.22(total 1H,s).

Example 1

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Among the components described below, 247.7 g of lansoprazole R-isomer (hereinafter, referred to as 'Compound A'), 184.6 g of magnesium carbonate, 492.2 g of purified sucrose, 299.9 g of corn starch and 329.6 g of low substituted hydroxypropyl cellulose were mixed well to obtain a dusting powder. 880 g of sucrose starch spheres (trade name: Nonpareil-101, produced by Freund Industrial Co., Ltd.) were charged in a centrifugal fluid-bed granulator (CF-360, manufactured by Freund Industrial Co., Ltd.) and the above dusting powder was coated on the sucrose starch spheres while spraying a hydroxypropyl cellulose solution (2 w/w%), thereby producing spherical granules. The spherical granules were dried at 40°C for 16 hrs under vacuum and passed through a round sieve to give

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1.4 mg 300.0 mg 36.4 mg 40.0 mg 59.8 mg 110.0 mg 30.0 mg 22.4 mg Composition in 300.0 mg of the granules low substituted hydroxypropyl cellulose hydroxypropyl cellulose sucrose starch spheres magnesium carbonate purified sucrose corn starch Compound A total 10

Example 2

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dissolved in 1206 g of purified water, and 78 g of talc, 25 g of titanium oxide and 866.7 g of methacrylic acid copolymer LD (260 g as solid content) were dispersed into the resulting solution to obtain an enteric coating solution. The granules obtained in Example 1 were coated with the above enteric coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 45°C, rotor revolution speed: 200 rpm, coating solution spray rate: 3.8 g/min. and spray air pressure: 1.0 kg/cm², followed by drying as it was and passing through a round sieve to give enteric-coated

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granules of 710  $^{\mu}\text{m-1400}^{\mu}\text{m}$  having following composition. The obtained spherical granules were dried at 40°C for 16 hrs under vacuum. Composition in 369.2 mg of the enteric-coated granules 300.0 mg methacrylic acid copolymer LD granules of Example 1

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148.7.mg (44.6 mg as solid

content)

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4.4 mg 13.8 mg 4.4 mg 2.0 mg 369.2 mg titanium oxide Polysorbate 80 Macrogol 6000 total talc

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Example 3

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were dissolved in a mixed solution of purifiec water (69.12 speed: 150 rpm, coating solution spray rate: 3.3.g/min. and methacrylic acid copolymer L and 4.8 g of triethyl citrate solution. 100 g of the enteric-coated granules obtained in Example 2 was coated with the above coating solution using condition of inlet air temperature: 30°C, rotor revolution dispersed into the resulting solution to obtain a coating and absolute ethanol (622.08 g), and 24 g of talc was manufactured by Freund Industrial Co., Ltd.) under the an agitation fluidized bed granulator (SPIR-A-FLOW, 36 g of methacrylic acid copolymer S, 12 g of

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Then the obtained spherical granules were dried at 40°C for sieve to give controlled release granules of 713 $\mu_m$ -1403 $\mu_m$ . granules having the following composition which is coated spray air pressure: 1.0 kg/cm² to give controlled release resulting spherical granules were passed through a round with release-controlled coating-layer being soluble pHdependently (releasing an active ingredient under the circumstances of more than a certain pH value). The 16 hrs under vacuum.

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Composition in 605.5 mg of the controlled release granules 369.2 mg 110.8 mg 36.9 mg 73.8 mg 14.8 mg 605.5 mg enteric-coated granules of Exampie 2 nethacrylic acid copolymer S methacrylic acid copolymer I triethyl citrate total talc

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Example 4

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were dissolved in a mixed solution of purified water (69.12 methacrylic acid copolymer L and 4.8 g of triethyl citrate solution. 100 g of the enteric-coated granules obtained in Example 2 was coated with the above coating solution using g) and absolute ethanol (622.08 g), and 24 g of talc was dispersed into the resulting solution to obtain coating 24 g of methacrylic acid copolymer S, 24 g of

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speed: 150 rpm, coating solution spray rate: 3.3 g/min. and Then the obtained spherical granules were dried at  $40^{\circ}\text{C}$  for rotor revolution sieve to give controlled release granules of  $710 \mu m - 1400 \mu m$  . granules having the following composition which is coated spray air pressure: 1.0 kg/cm² to give controlled release resulting spherical granules were passed through a round with release-controlled coating-layer being soluble pHmanufactured by Freund Industrial Co., Ltd.) under the dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The an agitation fluidized bed granulator (SPIR-A-FLOW, condition of inlet air temperature: 30°C, 16 hrs under vacuum.

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Composition in 605:5 mg of the controlled release granules 14.8 mg 605.5 mg 369.2 mg 73.85 mg 73.85 mg 73.8 mg enteric-coated granules of Example methacrylic acid copolymer S methacrylic acid copolymer L triethyl citrate total talc

Example 5

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104 mg of enteric-coated granules obtained in Example controlled release granules obtained in Example 3 were mixed and thereto 205 mg of polyethylene of 500 mg and

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oxide (trade name: Polyox WSR Coagulant, produced by Dow a mixture. Two geratin capsules #0 were filled with the resulting mixture obtain Chemical Co., Ltd.) was added to to obtain a capsule.

Example 6

104 mg of enteric-ccated granules obtained in Example mg of controlled release granules obtained in of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow geratin capsules #0 were filled with the resulting mixture a mixture. Chemical Co., Ltd.) was added to obtain Example 4 were mixed and thereto 205 mg to obtain a capsule. 500 and

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Example 7

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30C g of Compound A, 105 g of magnesium carbonate, 195 hydroxypropyl cellulose were mixed well to obtain a dusting sucrose starch spheres (trade name: Nonpareil-101, produced Freund Industrial Co., Ltd.) and the sucrose starch spheres obtain a dusting powder for intermediate layer. 375 g of manufactured by substituted hydroxypropyl cellulose were mixed well to powder for active ingredient layer. 75 g of purified were coated with the above dusting powder for active sucrose, 48.8 g of titanium oxide and 18.8 g of low g of purified sucrose and 75 g of .low substituted by Freund Industrial Co., Ltd.) were charged in a centrifugal fluid-bedgranulator (CF-360,

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ingredient layer while spraying a hydroxypropyl cellulose solution (2 w/w%), thereby producing spherical granules. Then, the resulting spherical granules were coated with the above dusting powder for intermediate layer while spraying a hydroxypropyl cellulose solution (2 w/w%) to obtain spherical granules. The obtained spherical granules were dried at 40°C for 16 hrs under vacuum and passed through a round sieve to give granules of 710½m-1400½m.

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0.75 mg 120.0 mg 7.5 mg 37.5 mg 30.0 mg 10.5 mg щg 4.875 mg 7.5 mg 1.875 mg 19.5 dusting powder for active ingredient layer Composition in 120.0 mg of the granules low substituted hydroxypropyl cellulose low substituted hydroxypropyl cellulose dusting powder for intermediate layer hydroxypropyl cellulose sucrose starch spheres magnesium carbonate purified sucrose purified sucrose titanium oxide Compound A total

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25 g of Macrogol 6000 and 10 g of Polysorbate 80 were dissolved in 1206 g of purified water, and 78 g of talc, 25

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Example 8

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with the above enteric coating solution using an agitation composition. The obtained spherical granules were dried at copolymer LD (260 g as solid content) were dispersed into Freund Industrial Co., Ltd.) under the condition of inlet solution. The granules obtained in Example 7 were coated fluidized bed granulator (SPIR-A-FLOW, manufactured by air temperature: 45°C, rotor revolution speed: 200 rpm, pressure: 1.0 kg/cm², followed by drying as it was and coating solution spray rate: 3.8 g/min. and spray air passing through a round sieve to give enteric-coated g of titanium oxide and 866.7 g of methacrylic acid the resulting solution to obtain an enteric coating granules of 710 4m-1400 4m having the following 40°C for 16 hrs under vacuum. Ŋ 9

mg (19.5 mg as solid Composition in 149.86 mg of the enteric-coated granules 5.85 mg 120.00 mg 1.88 mg 149.86 mg 1.88 mg 0.75 mg 65 methacrylic acid copolymer LD granules of Example 7 Polysorbate 80 titanium oxide Macrogol 6000 content) total talc 20

Example 9

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were dissolved in a mixed solution of purified water (69.12 speed: 150 rpm, coating solution spray rate: 3.3 g/min. and methacrylic acid copolymer L and 4.8 g of triethyl citrate solution. 100 g of the enteric-coated granules obtained in Example 8 was coated with the above coating solution using  $^{\mu}_{m}.$  Then the obtained spherical granules were dried at 40°C condition of inlet air temperature: 30°C, rotor revolution dispersed into the resulting solution to obtain a coating granules having the following composition which is coated spray air pressure: 1.0 kg/cm² to give controlled release g) and absolute ethanol (622.08 g), and 24 g of talc was with a release-controlled coating-layer being soluble pHresulting spherical granules were passed through a round sieve to give controlled release granules of 710  $\mu_m{-}1400$ manufactured by Freund Industrial Co., Ltd.) under the dependently (releasing an active ingredient under the an agitation fluidized bed granulator (SPIR-A-FLOW, circumstances of more than a certain pH value). The 36 g of methacrylic acid copolymer S, 12 g of for 16 hrs under vacuum.

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Composition in 245.86 mg of the controlled release granules enteric-coated granules of Example 8 149.86 mg methacrylic acid copolymer S 45.00 mg methacrylic acid copolymer L 15.00 mg

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talc 30.00 mg
triethyl citrate 6.00 mg
total 245.86 mg

Example 10

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were dissolved in a mixed solution of purified water (69.12 speed: 150 rpm, coating solution spray rate: 3.3 g/min. and Then the obtained spherical granules were dried at 40°C methacrylic acid copolymer L and 4.8 g of triethyl citrate solution. 100 g of the enteric-coated granules obtained in Example 8 was coated with the above coating solution using condition of inlet air temperature: 30°C, rotor revolution dispersed into the resulting solution to obtain a coating granules having the following composition which is coated spray air pressure: 1.0 kg/cm² to give controlled release with a release-controlled coating-layer being soluble pHg) and absolute ethanol (622.08 g), and 24 g of talc was resulting spherical granules were passed through a round sieve to give controlled release granules of 710 Hm-1400 manufactured by Freund Industrial Co., Ltd.) under the dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The an agitation fluidized bed granulator (SPIR-A-FLOW, 24 g of methacrylic acid copolymer S, 24 g of for 16 hrs under vacuum.

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Composition in 245.86 mg of the controlled release granules 6.0 mg 30.0 mg 30.0 mg 30.0 mg 149.86 mg enteric-coated granules of Example 8 methacrylic acid copolymer S methacrylic acid copolymer L triethyl citrate talc

Example 11

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245.86 mg

Dov 35.5 mg of enteric-coated granules obtained in Example 8 and 175 mg of controlled release granules obtained in Example 9 were mixed and thereto 70.2 mg of polyethylene Chemical Co., Ltd.) was added to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain oxide (trade name: Polyox WSR Coagulant, produced by a capsule (correspond to 30 mg of Compound A). Example 12

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35.5 mg of enteric-coated granules obtained in Example of controlled release granules obtained in Example 10 were mixed and thereto 70.2 mg of polyethylene to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain produced by capsule (correspond to 30 mg of Compound A). oxide (trade name: Polyox WSR Coagulant, Chemical Co., Ltd.) was added 8 and 175 mg

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Experiment Example 1

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6hrs, 7 hrs, 8hrs and 10 hrs after administration was 186 of water to a fasting beagle dog. Each ng/mL, 132 ng/mL, 107 ng/mL, 303 ng/mL, 355 ng/mL, 216 plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, orally with 30 ml

Experiment Example 2

ng/mL and 113 ng/mL, respectively.

Each 7 hrs, 8hrs and 10 hrs after administration was 192 6 was administered 364 ng/mL, 257 plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, orally with 30 ml of water to a fasting beagle dog. ng/mL, 137 ng/mL, 473 ng/mL, 478 ng/mL, capsule obtained in Example ng/mL and 28 ng/mL, respectively. 6hrs,

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Experiment Example 3

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Each capsule obtained in Example 11 was administered ohrs, 7 hrs, 8hrs and 10 hrs after administration was 308 26 ng/mL plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, orally with 30 ml of water to a fasting beagle dog. ng/mT, 81 ng/mL, 39 323 ng/mL, and 0 ng/mL, respectively. 245 ng/mL, ng/mT,

Experiment Example 4 20

Each 6hrs, 7 hrs, 8hrs and 10 hrs after administration was 160 capsule obtained in Example 12 was administered 230 ng/mL, 144 orally with 30 ml of water to a fasting beagle dog. plasma concentration of Compound A at 1 hr, ng/mL, 319 ng/mL, 631 ng/mL, 371 ng/mL,

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in Example 5 was administered

capsule obtained

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were dissolved in a mixed solution of purified water (69.12 speed: 150 rpm, coating solution spray rate: 3.3 g/min. and  $^{\mu}\mathrm{m}.$  Then the obtained spherical granules were dried at 40°C methacrylic acid copolymer L and 4.8 g of triethyl citrate solution. 100 g of the enteric-coated granules obtained in Example heta was coated with the above coating solution using condition of inlet air temperature: 30°C, rotor revolution dispersed into the resulting solution to obtain a coating granules having the following composition which is coated spray air pressure: 1.C kg/cm² to give controlled release with a release-controlled coating-layer being soluble pHg) and absolute ethanol (622.08 g), and 24 g of talc was resulting spherical granules were passed through a round sieve to give controlled release granules of 710  $\ensuremath{\mbox{ Mn-}}\xspace-1400$ manufactured by Freund Industrial Co., Ltd.) under the dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The an agitation fluidized bed granulator (SPIR-A-FLOW, 36 g of methacrylic acid copolymer S, 12 g of ng/mL and 25 ng/mL, respectively. 324 for 16 hrs under vacuum. Example 13

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Composition in 221.86 mg of the controlled release granules 149.86 mg enteric-coated granules of Example 8

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	methacrylic acid copolymer S	33.75 mg
	methacrylic acid copolymer L	11.25 mg
	talc	22.5 mg
	triethyl citrate	4.5 mg
Ŋ	total	221.86 mg
	Example 14	
	24 g of methacrylic acid copolymer	r S, 24 g of
	methacrylic acid copolymer L and 4.8 $\ensuremath{\text{g}}$	of triethyl citrate
	were dissolved in a mixed solution of	purified water (69.12
10	g) and absolute ethanol (622.08 g), and	d 24 g of talc was
	dispersed into the resulting solution	to obtain a coating
	solution. 100 g of the enteric-coated	granules obtained in
	Example $\theta$ was coated with the above coating	ating solution using
	an agitation fluidized bed granulator	granulator (SPIR-A-FLOW,
15	manufactured by Freund Industrial Co.,	Ltd.) under the
	condition of inlet air temperature: 30°	30°C, rotor revolution
	speed: 150 rpm, coating solution spray	spray rate: 3.3 g/min. and
	spray air pressure: 1.0 $kg/cm^2$ to give	controlled release
	granules having the following composition	ion which is coated
20	with a release-controlled coating-layer being	r being soluble pH-
	dependently (releasing an active ingredient	dient under the
•	circumstances of more than a certain p	pH value). The
	resulting spherical granules were passed	ed through a round
	sieve to give controlled release granules	Les of 710 $\mu_m$ -1400 $\mu_m$ .
25	Then the obtained spherical granules we	were dried at 40°C for

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hrs under vacuum. 16

Composition in 221.86 mg of the controlled release granules 4.5 mg 149.86 mg 22.5 mg 22.5 mg 22.5 mg 221.86 mg enteric-coated granules of Example 8 methacrylic acid copolymer S methacrylic acid copolymer L triethyl citrate

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Example 15

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35.5 mg of enteric-coated granules obtained in Example Dow to obtain a mixture. One and 168 mg of controlled release granules obtained in Example 13 were mixed and thereto 68.2 mg of polyethylene capsule #1 was filled with the resulting mixture to obtain oxide (trade name: Polyox WSR Coagulant, produced by a capsule (correspond to 30 mg of Compound A) Chemical Co., Ltd.) was added

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Example 16

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to obtain a mixture. One 35.5 mg of enteric-coated granules obtained in Example Dow of controlled release granules obtained in Example 14 were mixed and thereto 68.2 mg of polyethylene capsule #1 was filled with the resulting mixture to obtain oxide (trade name: Polyox WSR Coagulant, produced by a capsule (correspond to 30 mg of Compound A). Chemical Co., Ltd.) was added 8 and 168 mg

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Example 17

35.5 mg of enteric-coated granules obtained in Example 8 and 168 mg of controlled release granules obtained in Example 13 were mixed and the resulting mixture was filled ŏ in one capsule #3 to give a capsule (correspond to 30 mg Compound A).

Example 18

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Example 14 were mixed and the resulting mixture was filled οţ 35.5 mg of enteric-coated granules obtained in Example controlled release granules obtained in in one capsule #3 to give a capsule (correspond to 30 mg of шg Compound A). and 168

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Experiment Example 5

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capsule obtained in Example 14 was administered Each 6hrs, 7 hrs, 8hrs and 10 hrs after administration was 403 ng/mL, 217 plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, orally with 30 ml of water to a fasting beagle dog. 329 ng/mI, ng/mL, 687 ng/mL, 803 ng/mL, 463 ng/mL and 65 ng/mL, respectively.

Example 19 20

Co., Ltd.) and Ac-Di-Sol ratio of 32 w/w% based on the granules while spraying a charged in a centrifugal fluid-bed granulator (CF-mini, that is a disintegrant were coated on the granules by 100 g of the granules obtained in Example 1 was manufactured by Freund Industrial

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solution of hydroxypropyl cellulose dissolved in isopropyl alcohol (8 w/w%), thereby producing spherical granules. The spherical granules were dried at 40°C for 16 hrs under vacuum and passed through a round sieve to give granules of 1400½m or less.

Example 20

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revolution speed: 150 rpm, coating solution spray rate: 3.1 dissolved in acetone (120 g) and isopropyl alcohol (288 g), solution using an agitation fluidized bed granulator (SPIRand 48 g of talc was dispersed into the resulting solution A-FLOW, manufactured by Freund Industrial Co., Ltd.) under of 710 $\mu$ m-1700 $\mu$ m. Then the obtained spherical granules were composition. The resulting spherical granules were passed sieve to give controlled release granules obtained in Example 19 was coated with the above coating 24 g of aminoalkyl methacrylate copolymer RS was to obtain a coating solution. 100 g of the granules the condition of inlet air temperature: 30°C, rotor g/min. and spray air pressure: 1.0 kg/cm² to give controlled release granules having the following dried at 40°C for 16 hrs under vacuum. through a round

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Composition in 130.0 mg of the controlled release granules granules of Example 19 100 mg aminoalkyl methaczylate copolymer RS 10.0 mg

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20.0 mg	130.0 mg
talc	total

Example 21

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2 and 420 mg of controlled release granules obtained in Example Example 20 were mixed and thereto 175 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. Two gelatin capsules #0 were filled with the resulting mixture to obtain a capsule (correspond to 30 mg of Compound A).

Example 22

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104 mg of enteric-coated granules obtained in Example 2 and 420 mg of controlled release granules obtained in Example 20 were mixed and the resulting mixture was filled in two gelatin capsules #0 to give a capsule (correspond to 30 mg of Compound A).

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Experiment Example 6

A capsule obtained in Example 21 was administered orally with 30 ml of water to a fasting beagle dog. Each plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, 6hrs, 7 hrs, 8hrs and 10 hrs after administration was 657 ng/mL, 406 ng/mL, 223 ng/mL, 504 ng/mL, 399 ng/mL, 228 ng/mL and 50 ng/mL, respectively.

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Example 23

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36 g of methacrylic acid copolymer S, 12 g of

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were dissolved in a mixed solution of purified water (69.12 solution. 100 g of the granules obtained in Example 19 was dispersed into the resulting solution to obtain a coating coated with the above coating solution using an agitation Freund Industrial Co., Ltd.) under the condition of inlet having the following composition. The resulting spherical g) and absolute ethanol (622.08 g), and 24 g of talc was obtained spherical granules were dried at 40°C for 16 hrs pressure: 1.0 kg/cm² to give controlled release granules controlled release granules of 710  $\mbox{\sc Hm--}\mbox{\sc 1700}$   $\mbox{\sc \mum.}$  Then the air temperature: 30°C, rotor revolution speed: 150 rpm, fiuidized bed granulator (SPIR-A-FLOW, manufactured by coating solution spray rate: 3.3 g/min. and spray air granules were passed through a round sieve to give under vacuum

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Composition in 164.0 mg of the controlled release granules 4.0 mg 30.0 mg 10.0 mg 20.0 mg 100 mg 164.0 mg nethacrylic acid copolymer S methacrylic acid copolymer L granules of Example 19 triethyl citrate total talc

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methacrylic acid copolymer L and 4.8 g of triethyl citrate

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104 mg of enteric-coated granules obtained in Example mg of controlled release granules obtained in Example 23 were mixed and thereto 239 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. Two gelatin capsules #0 were filled with the resulting mixture to obtain a capsule (correspond to 30 mg of Compcund A). and 614 Example 25 104 mg of enteric-ccated granules obtained in Example Example 23 were mixed and the resulting mixture was filled granules obtained in in two gelatin capsules #0 to obtain a capsule (correspond release controlled to 30 mg of Compound A). 614 mg of and N

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Experiment Example 7

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capsule obtained in Example 24 was administered 6hrs, 7 hrs, 8hrs and 10 hrs after administration was 106 orally with 30 ml of water to a fasting beagle dog. Each 639 ng/ml, 129 ng/ml, 49 ng/ml, 16 ng/ml plasma concentration of Compound A at 1 hr, 2 hrs, 4 hrs, and 0 ng/mL, respectively. ng/mL, 135 ng/mL,

Comparison Example 1

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One gelatin capsule #0 obtained in Example 2, which acministered orally with 30 ml of water to a fasting beagle granules, enteric-coated of БЩ 414 was filled with

dog. Each plasma concentration of Compound A at 1 hr, 2 hrs,

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Example 24

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4 hrs, 6hrs, 7 hrs, 8hrs and 10 hrs after administration was 2,068 ng/mL, 689 ng/mL, 70 ng/mL, 0 ng/mL, 0 ng/mL, 0 ng/mL and 0 ng/mL, respectively.

Example 26

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of low substituted hydroxypropyl cellulose and 25 g of hydroxypropyl cellulose were suspended in 1420 g of purified water to obtain a spraying solution. 200 g of crystalline cellulose (sphere) was charged in an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund industrial Co., Ltd.) and was sprayed with the above spraying solution under the condition of inlet air temperature: 62°C, rotor revolution speed: 300 rpm, coating solution spray rate: 10 g/min. and spray air pressure: 1.0 kg/cm² to give spherical granules having the following composition. The resulting spherical granules were dried at 40°C for 16 hrs under vacuum and passed through a round sieve to give controlled release granules of 500 µm-1400 µm.

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Composition in 41.24 mg of the granules

crystalline cellulose (sphere) 22.5 mg

Compound A 11.25 mg

magnesium carbonate 3.75 mg

low substituted hydroxypropyl cellulose 10.0 mg

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	hydroxypropyl cellulose	1.87 mg
	total	41.24 mg
	Example 27	
	90 g of Compound A, 31.5 g of magnesium	ium carbonate,
ιΩ	58.5 g of purified sucrose and 22.5 g of low	low substituted
	hydroxypropyl cellulose were mixed well to	to obtain a dusting
	powder of active ingredient layer. 110 g	of the granules
	obtained in Example 26 was charged in a $\sigma$	centrifugal fluid-
	bed granulator (CF-mini, manufactured by Freund Industrial	reund Industrial
10	Co., Ltd.) and was coated with the above dusting	dusting powder of
	active ingredient layer while spraying a	hydroxypropyl
	cellulose solution (2 $\text{w/w\$}$ ), thereby producing	scing spherical
	granules having the following composition. The	The obtained
	spherical granules were dried at 40°C for 16 hrs	16 hrs under
15	vacuum and passed through a round sieve to	give granules of
	7104m-14004m.	

Composition in 118.03 mg of the granules	
granules of Example 26	41.25
Compound A	33.75
magnesium carbonate	11.81
purified sucrose	21.94
low substituted hydroxypropyl cellulose	8.44
hydroxypropyl cellulose	0.84

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118.03 mg

total

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#### Example 28

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Freund Industrial Co., Ltd.), and were dried intact to give speed: 200 rpm, coating solution spray rate: 3.0 g/min. and solution for intermediate layer was produced by dissolving coating solution for intermediate layer using an agitation The granules obtained in Example 27 were coated with 20.09 g of hydroxypropyl methylcellulose 2910 in 362.55 g condition of inlet air temperature: 62°C, rotor revolution solution. The coating operation was carried out under the passed through a round sieve to give granules of 710  $^{
m Hm-}$ granules were dried at 40°C for 16 hrs under vacuum and spray air pressure:  $1.0 \, \mathrm{kg/cm}^2$ . The resulting spherical fluidized bed granulator (SPIR-A-FLOW, manufactured by granules having the following composition. The coating of purified water and followed by dispersing 8.03 g of titanium oxide and 12.05 g of talc into the obtained 1400 µm

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Composition in 133.03 mg of the granules coated with an intermediate layer
granules of Example 27 118.03 mg
hydroxypropyl methylcellulose 2910 7.5 mg
talc
talc 4.5 mg
titanium oxide 3.0 mg

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133.03 mg

total

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Example 29

dissolved in 1206 g of purified water, and 78 g of talc, 25 g of titanium oxide and 866.7 g of methacrylic acid copolymer LD (260 g as solid content) were dispersed into the resulting solution to obtain an enteric coating solution. The granules obtained in Example 28 were coated with the above enteric coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltd.) under the condition of inlet air temperature: 45°C, rotor revolution speed: 200 rpm, coating solution spray rate: 3.8 g/min. and spray air pressure: 1.0 kg/cm², followed by drying as it was and passing through a round sieve to give enteric-coated granules of 710 Pm-1400 Pm having the following composition. The obtained spherical granules were dried at

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Composition in 165.18 mg of the enteric-coated granules granules of Example 28 133.03 mg methacrylic acid copolymer LD 70 mg (21 mg as solid content)

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40°C for 16 hrs under vacuum.

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talc 6.30 mg

Macrogol 6000 2.02 mg

25 titanium oxide 2.02 mg

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were dissolved in a mixed solution of purified water (69.12  $\mu_{m}.$  Then the obtained spherical granules were dried at  $40^{\circ}\mathrm{C}$ methacrylic acid copolymer L and 4.8 g of triethyl citrate solution. 100 g of the granules obtained in Example 28 was rpm, coating solution spray rate: 3.0 g/min. and spray air dispersed into the resulting solution to obtain a coating coated with the above coating solution using an agitation sieve to give controlled release granules of 1180 Pm-1700 g) and absolute ethanol (622.08 g), and 24 g of talc was resulting spherical granules were passed through a round pressure: 1.0 kg/cm2 to give controlled release granules having the following composition which is coated with a inletair temperature: 30°C, rotor revolution speed: 100 fluidized bed granulator (SPIR-A-FLOW, manufactured by dependently (releasing an active ingredient under the Freund Industrial Co., Ltd.) under the condition of circumstances of more than a certain pH value). The 36 g of methacrylic acid copolymer S, 12 g of release-controlled coating-layer being solubie pH-0.81 mg 165.18 mg for 16 hrs under vacuum. Polysorbate 80 Example 30 total S 10 15 20

Composition in 196.88 mg of the controlled release granules

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	triethyl citrate 3.99 mg	talc 19.95 mg	methacrylic acid copolymer L 9.98 mg	methacrylic acid copolymer S 29.93 mg	granules of Example 28 133.03 mg	133.03 mg 29.93 mg 9.98 mg 19.95 mg	granules of Example 28 methacrylic acid copolymer S methacrylic acid copolymer L talc triethyl citrate
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Example 31

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were dissolved in a mixed solution of purified water (69.12 methacrylic acid copolymer L and 4.8 g of triethyl citrate solution. 100 g of the granules obtained in Example 28 was dispersed into the resulting solution to obtain a coating coated with the above coating solution using an agitation freund Industrial Co., Ltd.) under the condition of inlet g) and absolute ethanol (622.08 g), and 24 g of talc was resulting spherical granules were passed through a round pressure: 1.0 kg/cm² to give controlled release granules having the following composition which is coated with a fluidized bed granulator (SPIR-A-FLOW, manufactured by air temperature: 30°C, rotor revolution speed: 100 rpm, coating solution spray rate: 3.0 g/min. and spray air dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The 24 g of methacrylic acid copolymer S, 24 g of release-controlled coating-layer being soluble pH-

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sieve to give controlled release granules of 1180  $\ensuremath{\text{\mbox{\scriptsize Pm-1700}}}$ 

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 $\mu_{m}.$  Then the obtained spherical granules were dried at  $40^{\circ}\text{C}$ for 16 hrs under vacuum

Composition in 196.88 mg of the controlled release granules 133.03 mg 19.95 mg 19.95 mg 19.95 mg 3.99 mg 196.88 mg methacrylic acid copolymer S methacrylic acid copolymer L granules of Example 28 triethyl citrate total talc

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Example 32

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One and 98.7 mg of controlled release granules obtained in capsule #1 was filled with the resulting mixture to obtain of enteric-coated granules obtained in Example Example 30 were mixed and thereto 42.3 mg of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow to obtain a mixture. a capsule (correspond to 30 mg of Compound A) was added Ltd.) Chemical Co., . g 28 29

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Example 33

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of enteric-coated granules obtained in Example 29 and 98.7 mg of controlled release granules obtained in Example 31 were mixed and thereto 42.3 mg of polyethylene to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added БШ 28

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a capsule (correspond to 30 mg of Compound A). Example 34 mg of enteric-coated granules obtained in Example 29 and 197.4 mg of controlled release granules obtained in Example 30 were mixed and the resulting mixture was filled of in one capsule #2 to give a capsule (correspond to 60 mg Compound A)

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Example 35

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84 mg of enteric-coated granules obtained in Example Example 30 were mixed and the resulting mixture was filled granules obtained in in one capsule #1 to give a capsule (correspond to 90 mg of 29 and 296.1 mg of controlled release Compound A).

Example 36

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42 mg of enteric-coated granules obtained in Example 29 and 148.05 mg of controlled release granules obtained in Example 30 were mixed and the resulting mixture was filled of in one capsule #3 to give a capsule (correspond to 45 mg Compound A).

Example 37

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and 24 g of talc was dispersed into the resulting solution purified water (69.12 g) and absolute ethanol (622.08 g), 48 g of methacrylic acid copolymer S and 4.8 g of rriethyl citrate were dissolved in a mixed solution of to obtain a coating solution. 100 g of the granules

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obtained in Example 30 was coated with the above coating solution using an agitation fluidized bed granulator (SPIR-A-FLOW, manufactured by Freund Industrial Co., Ltc.) under the condition of inlet air temperature: 30°C, rotor revolution speed: 100 rpm, coating solution spray rate: 3.0 g/min. and spray air pressure: 1.0 kg/cm² to give controlled release granules having the following composition which is coated with a release-controlled coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were passed through a round sieve to give controlled release granules of 1180 Pm-1700 Pm. Ther the obtained spherical granules were dried at 40°C for 16 hrs under vacuum.

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Composition in 207.52 mg of the controlled release granules granules of Example 30 196.88 mg
methacrylic acid copolymer S 6.65 mg
talc
triethyl citrate 0.67 mg
total 207.52 mg

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48 g of methacrylic acid copolymer S and 4.8 g of triethyl citrate were dissolved in a mixed solution of purified water (69.12 g) and absolute ethanol (622.08 g),

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revolution speed: 100 rpm, coating solution spray rate: 3.0 solution using an agitation fluidized bed granulator (SPIRand 24 g of talc was dispersed into the resulting solution A-FLOW, manufactured by Freund Industrial Co., Ltd.) under obtained in Example 31 was coated with the above coating coating-layer being soluble pH-dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The resulting spherical granules were granules of 1180  $\mbox{\sc Hm}-1700\mbox{\sc Hm}.$  Then the obtained spherical passed through a round sieve to give controlled release composition which is coated with a release-controlled g of the granules granules were dried at 40°C for 16 hrs under vacuum. the condition of inlet air temperature: 30°C, rotor g/min. and spray air pressure: 1.0 kg/cm² to give controlled release granules having the following to obtain a ccating solution. 100 10 15

Composition in 207.52 mg of the controlled release granules granules of Example 31 196.88 mg methacrylic acid copolymer S 6.65 mg talc 3:32 mg triethyl citrate 0.67 mg total 207.52 mg

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Example 39

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28 mg of enteric-coated granules obtained in Example

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29 and 103.8 mg of controlled release granules obtained in of polyethylene oxide (trade name: Polyox WSR Coagulant, produced by Dow One capsule #1 was filled with the resulting mixture to obtain Chemical Co., Ltd.) was added to obtain a mixture. capsule (correspond to 30 mg of Compound A). Example 37 were mixed and thereto 43.9 mg

Example 40

S

mg of enteric-coated granules obtained in Example 29 and 103.8 mg of controlled release granules obtained in pclyethylene oxide (trade name: Folyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain of capsule (correspond to 30 mg of Compound A) Example 38 were mixed and thereto 43.9 mg

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Example 41

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56 mg of enteric-coated granules obtained in Example 29 and 207.5 mg of controlled release granules obtained in Example 37 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 60 mg of Compound A).

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Example 42

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mg of enteric-costed granules obtained in Example Example 37 were mixed and the resulting mixture was filled and 311.3 mg of controlled release granules obtained in in one capsule #1 to give a capsule (correspond to 90 mg of 84 29

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sieve to give granules of 710  $\mu_m$ -1400  $\mu_m$ .

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Compound A)

Example 43

mg of enteric-coated granules obtained in Example 29 and 155.6 mg of controlled release granules obtained in Example 37 were mixed and the resulting mixture was filled in one capsule #3 to give a capsule (correspond to 45 mg of Compound A)

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Example 44

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300 g of Compound A, 105 g of magnesium carbonate, 195 hydroxypropyl cellulose were mixed well to obtain a dusting in a centrifugal fluid-bed granulator (CF-360, manufactured 101, produced by Freund Industrial Co., Ltd.) were charged sucrose starch spherical granules (trade name: Nonpareilobtain a dusting powder for intermediate layer. 375 g of cellulose solution (2 w/w%), thereby producing spherical å 40°C for 16 hrs under vacuum and passed through a round t t ctive ingredient layer while spraying a hydroxypropyl by Freund Industrial Co., Ltd.) and the sucrose starch spheres were coated with the above dusting powder for powder for active ingredient layer. 75 g of purified granules. The obtained spherical granules were dried substituted hydroxypropyl cellulose were mixed well sucrose, 48.8 g of titanium oxide and 18.8 g of low g of purified sucrose and 75 g of low substituted

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0.20	
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0.57 mg 56.25 mg 45.00 mg 15.75 mg 29.25 mg 11.25 mg 158.07 mg dusting powder for active ingredient layer Composition in 158.07 mg of the granules low substituted hydroxypropyl cellulose hydroxypropyl cellulose sucrose starch spheres magnesium carbonate purified sucrose Compound A total

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Example 45

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Freund Industrial Co., Ltd.), and were dried intact to give speed: 200 rpm, coating solution spray rate: 3.0 g/min. and coating solution for intermediate layer using an agitation solution for intermediate layer was produced by dissolving The granules obtained in Example 44 were coated with condition of inlet air temperature: 62°C, rotor revolution 20.09 g of hydroxypropyl methylcellulose 2910 in 361.55 g solution. The coating operation was carried out under the granules having the following composition. The coating of purified water and followed by dispersing 8.03 g of spray air pressure: 1.0 kg/cm². The resulting spherical granules were dried at 40°C for 16 hrs under vacuum and fluidized bed granulator (SPIR-A-FLOW, manufactured by titanium oxide and 12.05 g of talc into the obtained

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passed through a round sieve to give granules of 710 Hm-1400 µm.

Composition in 188.07 mg of the granules coated with an intermediate layer S

158.07 mg 15.00 mg 9.00 mg 6.00 mg 188.07 mg hydroxypropyl methylcellulose 2910 granules of Example 44 titanium oxide total talc

Example 46

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were dissolved in a mixed solution of purified water (69.12 methacrylic acid copolymer L and 4.8 g of triethyl citrate solution. 100 g of the granules obtained in Example 45 was dispersed into the resulting solution to obtain a coating coated with the above coating solution using an agitation Freund Industrial Co., Ltd.) under the condition of inlet g) and absolute ethanol (622.08 g), and 24 g of taic was pressure: 1.0 kg/cm2 to give controlled release granules having the following composition which is coated with a fluidized bed granulator (SPIR-A-FLOW, manufactured by sir temperature: 30°C, rotor revolution speed: 100 rpm, coating solution spray rate: 3.0 g/min. and spray air 36 g of methacrylic acid copolymer S, 12 g of

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release-controlled coating-layer being soluble pH-

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 $\mu_{m}.$  Then the obtained spherical granules were dried at  $40^{\circ}\text{C}$ sieve to give controlled release granules of 1180  $\ensuremath{\text{\sc bm-1700}}$ resulting spherical granules were passed through a round dependently (releasing an active ingredient under the circumstances of more than a certain pH value). The for 16 hrs under vacuum.

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Composition in 278.35 mg of the controlled release granules 28.21 mg 5.64 mg 188.07 mg 42.32 mg 14.11 mg 278.35 mg ß methacrylic acid copolymer L methacrylic acid copolymer granules of Example 45 triethyl citrate total talc

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Example 47

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35.5 mg of enteric-coated granules obtained in Example Example 46 were mixed and thereto 58.2 mg of polyethylene 8 and 139.2 mg of controlled release granules obtained in oxide (trade name: Polyox WSR Coagulant, produced by Dow Chemical Co., Ltd.) was added to obtain a mixture. One capsule #1 was filled with the resulting mixture to obtain of Compound A). capsule (correspond to 30 mg

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Example 48

71 mg of enteric-coated granules obtained in Example 8 and 278.35 mg of controlled release granules obtained in

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Example 46 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 60 mg of Compound A).

Example 49

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in obtained in Example 46 were mixed and the resulting mixture granules was filled in two capsules #2 to give a capsule (correspond enteric-coated granules obtained controlled release of шg to 90 mg of Compound A). Example 8 and 417.5 oŧ шg 106.5

Example 50

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53.3 mg of enteric-coated granules obtained in Example 8 and 208.8 mg of controlled release granules obtained in Example 46 were mixed and the resulting mixture was filled 벙 in one capsule #2 tó give a capsule (correspond to 45 mg

Example 51

Compound A).

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hydroxypropyl cellulose were mixed well to obtain a dusting 324.4 g of Compound A, 303.2 g of magnesium carbonate, coated with the above dusting powder for active ingredient reund Industrial Co., Ltd.) were charged in a centrifugal 1062 g of purified sucrose and 228.2 g of low substituted Industrial Co., Ltd.) and the sucrose starch spheres were powder for active ingredient layer. 722.4 g of sucrose. starch spheres (trade name: Nonpareil-101, produced by fluid-bed granulator (CF-360, manufactured by Freund

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vacuum and passed through a round sieve to give granules of layer while spraying a hydroxypropyl cellulose solution (2 w/w%), thereby producing spherical granules. The obtained spherical granules were dried at 40°C for 16 hrs under 710 µm-1400 µm.

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Composition in 86.67 mg of the granules

sucrose·starch spheres	20.64 mg
hydroxypropyl cellulose	0.24 mg
dusting powder for active ingredient layer	
Compound A	22.50 mg
magnesium carbonate	8.25 mg
purified sucrose	28.83 mg
low substituted hydroxypropyl cellulose	6.21 mg
total	86.67 mg

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Example 52

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The granules obtained in Example 51 were coated with a water and followed by dispersing 163.5 g of titanium oxide having the foilowing composition. The coating solution for coating solution for intermediate layer using a fluid-bed Powrex Co., Ltd.), and were dried intact to give granules and 108 g of talc into the obtained solution. The coating intermediate layer was produced by dissolving 270.0 g of hydroxypropyl methylcellulose 2910 in 4874 g of purified fluidized bed coating machine (MP-10, manufactured by

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MPa and spray air volume: 90 Nl/nr. The resulting spherical solution spray rate: 12.0 g/min., spray air pressure: 0.28 operation was carried out under the condition of inlet air temperature: 67°C, inlet air volume: 1.5 m³/min., coating passed through a round sieve to give granules of 710  $^{
m \mu m-}$ granules were dried at 40°C for 16 hrs under vacuum and 1400 µm. เก

Composition in 97.50 mg of the granules coated with an 86.67 mg 97.50 mg 5.40 mg 2.16 mg 3.27 mg hydroxypropyl methylcellulose 2910 granules of Example 51 intermediate layer titanium oxide total talc

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Example 53

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57.60 g of Macrogol 6000 and 26.40 g of Polysorbate 80 acid copolymer LD (579.6 g as solid content) were dispersed with the above enteric coating solution using an agitation talc, 57.6 g of titanium oxide and 19323 g of methacrylic solution. The granules obtained in Example 52 were coated were dissolved in 2724 g of purified water, and 174 g of into the resulting solution to obtain an enteric coating fluidized bed granulator (MP-10, manufactured by Powrex

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Co., Ltd.) under the condition of inlet air temperature:

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65°C, inlet air volume: 1.5  $\rm m^3/min.$ , coating solution spray rate: 15.0 g/min. and spray air pressure: 0.30 MPa, and spray air volume: 90 NI/hr. The resulting granules were dried as it was and passed through a round sleve to give enteric-coated granules of 710  $\rm \mu m$ -1400  $\rm ^{4}m$  having the following composition. The obtained spherical granules were dried at 40°C for 16 hrs under vacuum, and to 1918 g of the granules were added 0.96 g of talc and 0.96 g of aerosil to give enteric-coated granules.

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48.3 mg (14.49 mg as solid Composition in 120.0 mg of the enteric-coated granules 120.0 mg 97.5 mg 4.35 mg 1.44 mg 1.44 mg 0.66 mg 0.06 mg 0.06 mg methacrylic acid copolymer LD granules of Example 52 titanium oxide Polysorbate 80 Macrogol 6000 total content) aerosil talc talc

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Example 54

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1131 g of Compound A, 303.2 g of magnesium carbonate, 750.1 g of purified sucrose and 226.8 g of low substituted hydroxypropyl cellulose were mixed well to obtain a dusting

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powder for active ingredient layer. 720.3 g of sucrosestarch spheres (trade name: Nonpareil-101, produced by
Freund Industrial Co., Ltd.) were charged in a centrifugal
fluid-bed granulator (CF-360, manufactured by Freund
Industrial Co., Ltd.) and the sucrose-starch spheres were
coated with the above dusting powder for active ingredient
layer while spraying a hydroxypropyl cellulose solution (2
w/w%), thereby producing spherical granules. The obtained
spherical granules were dried at 40°C for 16 hrs under
vacuum and passed through a round sleve to give granules of
710 Pm-1400 Pm.

13.5 mg 189.0 mg 45.0 mg 0.54 mg 67.5 mg 18.0 mg 44.46 mg dusting powder for active ingredient layer Composition in 189.0 mg of the granules low substituted hydroxypropyl cellulose hydroxypropyl cellulose sucrose starch spheres magnesium carbonate purified sucrose Compound A Example 55 total 15 20

The granules obtained in Example 54 were coated with a coating solution for intermediate layer using a fluid-bed fluidized bed coating machine (MP-10, manufactured by

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Powrex Co., Ltd.), and were dried intact to give granules having the following composition. The coating solution for intermediate layer was produced by dissolving 236.4 g of hydroxypropyl methylcellulose 2910 in 4255 g of purified water and followed by dispersing 141.6 g of titanium oxide and 94.8 g of talc into the obtained solution. The coating operation was carried out under the condition of inlet air temperature: 65°C, inlet air volume: 1.5 m³/min., coating sclution spray rate: 12.0 g/min., spray air pressure: 0.26 MPa and spray air volume: 90 Nl/hr. The resulting spherical granules were dried at 40°C for 16 hrs under vacuum and passed through a round sieve to give granules of 710  $\mu_{\rm m}$ -1400  $\mu_{\rm m}$ .

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ß

Composition in 212.64 mg of the granules coated with an intermediate layer

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granules of Example 54 189.0 mg
hydroxypropyl methylcellulose 2910 11.82 mg
talc
titanium oxide 7.08 mg
total 212.64 mg

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Example 56

382.8 g of methacrylic acid copolymer S, 127.7 g of methacrylic acid copolymer L and 50.88 g of triethyl citrate were dissolved in a mixed solution of purified

of talc was dispersed into the resulting solution to obtain a coating solution. The granules obtained in Example 55 was or 16 hrs under vacuum, and to 1101 g of the granules were water (734.8 g) and absolute ethanol (6614 g), and 255.1 g  $^{\mathsf{J}}\mathsf{m}.$  Then the obtained spherical granules were dried at 40°C 65°C, inlet air volume: 1.5 m³/min., coating solution spray coated with the above coating solution using an agitation rate: 15.0 g/min., spray air pressure: 0.30 MPa and spray sieve to give controlled release granules of 1180 Pm-1700 air volume: 90 NI/hr to give controlled release granules resulting spherical granules were passed through a round Cc., Ltd.) under the condition of inlet air temperature: fluidized bed granulator (MP-10, manufactured by Powrex having the following composition which is coated with a dependently (releasing an active ingredient under the added 0.525 g of talc and 0.525 g of aerosil to give circumstances of more than a certain pH value). The release-controlled coating-layer being soluble pHenteric-coated granules. S 10 15

Composition in 315.0 mg of the controlled release granules

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granules or Example 55	ZIZ. 64 mg
methacrylic acid copolymer S	47.85 mg
methacrylic acid copolymer L	15.96 mg
talc	31.89 mg

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triethyl citrate 6.36 mg

talc 0.15 mg

aerosil 0.15 mg

total 315.0 mg

Example 57

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120 mg of enteric-coated granules obtained in Example 53 and 315 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 90 mg of

Example 58

Compound A)

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80 mg of enteric-coated granules obtained in Example 53 and 210 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 60 mg of Compound A).

Example 59

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40 mg of enteric-coated granules obtained in Example 53 and 105 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #3 to give a capsule (correspond to 30 mg of Compound A).

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Example 60

240 mg of enteric-coated granules obtained in Example 53 and 210 mg of controlled release granules obtained in

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Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 90 mg of Compound A).

Example 61

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160 mg of enteric-coated granules obtained in Example 53 and 280 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 90 mg of Compound A).

10 Example 62

192 mg of enteric-coated granules obtained in Example 53 and 252 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 90 mg of Compound A).

Example 63

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160 mg of enteric-coated granules obtained in Example 53 and 210 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 75 mg of Compound A).

Example 64

100 mg of enteric-coated granules obtained in Example 53 and 262.5 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled

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in one capsule #1 to give a capsule (correspond to 75 mg of Compound A).

Example 65

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Example 53 and 233.3 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 75 mg of Compound A).

Example 66

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200 mg of enteric-coated granules obtained in Example 53 and 175 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #1 to give a capsule (correspond to 75 mg of Compound A).

Example 67

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Example 53 and 186.7 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond

to 60 mg of Compound A).

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Example 68

128 mg of enteric-coated granules obtained in Example 53 and 168 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 60 mg of

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Compound A).

Example 69

16C mg of enteric-coated granules obtained in Example 53 and 140 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 60 mg of Compound A).

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Example 70

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60 mg of enteric-coared granules obtained in Example 53 and 157.5 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 45 mg of Compound A).

Example 71

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12C mg of enteric-coated granules obtained in Example 53 and 105 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 45 mg of Compound A).

20 Example 72

80 mg of enteric-coated granules obtained in Example 53 and 140 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 45 mg of

Compound A).

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Example 73

96 mg of enteric-coated granules obtained in Example 53 and 126 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #2 to give a capsule (correspond to 45 mg of Compound A).

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Example 74

53.3 mg of enteric-coated granules obtained in Example 53 and 93.3 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #3 to give a capsule (correspond to 30 mg of Compound A).

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Example 75

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64 mg of enteric-coated granules obtained in Example 53 and 84 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #3 to give a capsule (correspond to 30 mg of Compound A).

Example 76

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80 mg of enteric-coated granules obtained in Example 53 and 70 mg of controlled release granules obtained in Example 56 were mixed and the resulting mixture was filled in one capsule #3 to give a capsule (correspond to 30 mg of Compound A).

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Industrial Applicability

Since the controlled release preparation of the present invention can extend the therapeutic effective level by controlling the release of active ingredient over a long time, it can provide the effectiveness of treatment with a low dose and the reduction of side effects caused by the rise of blood leve, as well as the reduction of administration times.

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#### CLAIMS

1. A capsule comprising a tablet, granule or fine granule wherein the release of active ingredient is controlled and a gel-forming polymer.

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- 2. The capsule according to claim 1, wherein the release of active ingredient is controlled by a release-controlled coating-layer formed on a core particle containing an active ingredient.
- 3. The capsule according to claim 2, wherein the release-controlled coating-layer contains a pH-dependently soluble polymer.

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 The capsule according to claim 2, wherein the release-controlled ccating-layer is a diffusion-controlled layer.

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5. The capsule according to claim 1, wherein the release of active ingredient is controlled by dispersing an active ingredient into a release-controlled matrix composing tablet, granule or fine granule.

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the tablet, granule or fine granule in which the release of active ingredient is controlled has a disintegrant layer containing disintegrant formed on the core particle containing an active ingredient and a release-controlled coating-layer formed on said disintegrant layer, and the

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release of active ingredient is initiated after a certain lag time.

- 7. The capsule according to any one of claims 3 to 6, wherein the tablet, granule or fine granule in which the release of active ingredient is controlled is coated with a gel-forming polymer.
- 8. The capsule according to claim 7 which further contains a gel-forming polymer.
- 9. The capsule according to any one of claims 1 to 7, which comprises two kinds of tablet, granule or fine granule having different release properties of active ingredient.

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10. The capsule according to claim 9, which comprises a tablet, granule or fine granule having an enteric coat that releases an active ingredient at the pH of about 5.5 and a tablet, granule or fine granule having a release-controlled coating-layer that releases an active ingredient at the pH of about 6.0 or above.

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- 11. The capsule according to claim 1, 7 or 8, wherein 20 the gel-forming polymer is a polymer whose viscosity of 5% aqueous solution is about 3,000 mPa·s or more at 25°C.
- 12. The capsule according to claim 1, 7 or 8, wherein the gel-forming polymer is a polymer having molecular weight of 400,000 to 10,000,000.
- 13. The capsule according to any one of claims 2 to 4

or 6, wherein the release-controlled coating-layer is a layer containing one or more kinds of polymeric substances selected from the group consisting of hydroxypropylmethyl carboxymethylethyl cellulose, methyl methacrylatemethacrylic acid copolymer, methacrylic acid-ethyl acrylate methyl methacrylate-ethyl acrylate copolymer, methacrylic phthalate, methacrylatetrimethylammoniumethyl methacrylate chloride copolymer, hydroxypropyl cellulose acetate succinate and polyvinyl copolymer, cellulose acetate methacrylate acrylate-methyl acid-methyl acrylate-methyl phthalate, ethyl acetate phthalate. cellulose copolymer,

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14. The capsule according to claim 13, wherein the release-controlled coating-layer is comprised of 2 or more kinds of layers.

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The capsule according to claim 1, wherein the release-controlled granule or fine granule has a particle size of about 100-1,500 µm. 15.

The capsule according to claim 1, wherein the active ingredient is a proton pump inhibitor (PPI). 16.

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The capsule according to claim 16, wherein the PPI is an imidazole compound represented by the formula 17.

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wherein ring C' is an optionally substituted benzene ring substituted alkoxy group or an optionally substituted amino monocyclic an optionally an optionally group, and Y represents a nitrogen atom or CH; or a salt substituted aralkyl group, acyl group or acyloxy group, R1,  $R^2$  and  $R^3$  are the same or different and are a hycrogen atom, aromatic thereof or an optically active isomer thereof. heterocyclic ring, R<sup>0</sup> is a hydrogen atom, dnosb, an optionally substituted optionally substituted alkyl

18. The capsule according to claim 17, wherein the imidazole compound is lansoprazole.

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The capsule according to claim 17, wherein PPI is optically active R-isomer of lansoprazole. 20. The capsule according to any one of claim 1, 7 or wherein the gel-forming polymer is one or more kinds of (HPMC), cellulose 400,000consisting (HPC), hydroxyethyl cellulose and carboxyvinyl polymer. molecular weight: carboxymethyl cellulose (CMC-Na), hydroxypropyl cellulose droab hydroxypropylmethyl selected from the polyethylene oxide (PEO, , (000,000,01 substances 15 20

The capsule according to any one of claim 1, 7 or

- 8, wherein the gel-forming polymer is polyethylene oxide (molecular weight: 400,000-10,000,000)
- to claim 1 or 8, wherein the gel-forming polymer is added as a powder, fine granule capsule according or granule.

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- 23. The capsule according to claim 3, wherein the pHmethacrylatemethyl is polymer methacrylic acid copolymer. dependently soluble
- particle A tablet, granule or fine granule wherein the containing an imidazole compound represented by the formula release of active ingredient is controlled, said tablet, core granule comprising fine or 24. granule :(II)

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wherein ring C' is an optionally substituted benzene ring substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH; or a salt monocyclic optionally an optionally and  $R^3$  are the same or different and are a hydrogen atom, substituted aralkyl group, acyl group or acyloxy group,  $\mathrm{R}^{1},$ an aromatic is a hydrogen atom, an optionally substituted alkyl group, substituted optionally heterocyclic ring, R° an or

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thereof or an optically active isomer thereof as an active ingredient, and

methyl methacrylate-methacrylic acid copolymer, methacrylic mixture of two or more kinds of polymeric substances having group a pH-dependently soluble release-controlled coating-layer acid-methyl hydroxypropyl cellulose acetate succinate, polyvinyl acetate phthalate phthalate, cellulose acetate phthalate, carboxymethylethyl celiulose, and shellac, and said polymeric substance is soluble in the polymeric substance or the cellulose release properties selected from methacrylic copolymer, hydroxypropylmethy; acid-ethyl acrylate copolymer, which comprises one kind of methacrylate range of 6.0 to 7.5 . acrylate-methyl of consisting different

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The tablet, granule or fine granule according to controlled coating-layer is formed on an intermediate layer releasesoluble the pH-dependently which is formed on a core particle. wherein claim 24, 25.

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The capsule comprising the tablet, granule fine granule according to claim 24.

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fine granule according to claim 24 and an enteric-coated granule or 27. The capsule comprising the tablet, tablet, granule or fine granule containing represented by the formula (I'). The tablet, granule or fine granule according to

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claim 24, wherein the active ingredient is lansoprazole.

- 29. The tablet, granule or fine granule according to claim 24, wherein the active ingredient is an optically active R-isomer of lansoprazole.
- 30. The tablet, granule or fine granule according to claim 24, wherein the active ingredient is an optically active S-isomer of lansoprazole.

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31. The tablet, granule or fine granule according to claim 24, wherein the active ingredient is a derivative of lansoprazole.

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- 32. The tablet, granule or fine granule according to claim 24, wherein the active ingredient is a derivative of optically active R-isomer of lansoprazole.
- 33. The tablet, granule or fine granule according to any one of claim 24, 25 or 28 to 32, comprising having an enteric coat on the core particle containing an active ingredient, a disintegrant layer containing disintegrant on said enteric coat and a release-controlled coating-layer on said disintegrant layer.

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34. The tablet, granule or fine granule according to any one of claim 28 to 33, which is coated with a gelforming polymer.

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35. An extended release capsule comprising the tablet, granule or fine granule according to any one of claim 28 to 32 and a gel-forming polymer.

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A tablet, granule or fine granule according to release-controlled release-controlled than the inner ingredient active щ ğ outermost coating-layer is soluble at higher wherein the release of more kinds celease-controlled coating-layer. the or and ₽. coating-layers, ρλ controlled claim 24 36.

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claim 36, wherein the inner release-controlled coating-layer is soluble in the pH range of 6.0-7.0 and the outermost release-controlled coating-layer is soluble at the pH of 7.0 or above.

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38. The tablet, granule or fine granule according to claim 36, wherein the inner release-controlled coating-layer is soluble in the pH range of 6.5-7.0 and the outermost release-controlled coating-layer is soluble at the pH of 7.0 or above.

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39. The tablet, granule or fine granule according to claim 36, wherein the thickness of the outermost release-controlled coating-layer is 100 µm or less.

20 40. The granule or fine granule according to claim 36, wherein the release-controlled granule or fine granule has a particle size of about 100-1,500 µm.

41. A capsule comprising

(i) a tablet, granule or fine granule in which the release of active ingredient is controlled; said tablet, granule or

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fine granule comprises

a core particle containing an imidazole compound represented by the formula (I'):

wherein ring C' is an optionally substituted benzene ring or an optionally substituted aromatic monocyclic heterocyclic ring, R° is a hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R¹, R² and R³ are the same or different and are a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH; or a salt thereof or an optically active isomer thereof as an active ingredient, and

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a pH-dependently soluble release-controlled coating-layer which comprises one kind of polymeric substance or a mixture of two or more kinds of polymeric substances having different release properties selected from the group consisting of hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, carboxymethylethyl cellulose, methyl methacrylate-methacrylic acid copolymer, methacrylic acid-methyl

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acrylate-methyl methacrylate copolymer, hydroxypropyl cellulose acetate succinate, polyvinyl acetate phthalate and shellac; said polymeric substance is soluble in the pH range of 6.0 to 7.5, and

- 5 (ii) a tablet, granule or fine granule comprising a core particle containing an active ingredient and enteric coat which is dissolved, thereby an active ingredient being released in the pH range of no less than 5.0, nor more than 6.0.
- 10 42. The capsule according to claim 41, wherein the pH-dependently soluble release-controlled coating-layer is formed on an intermediate layer which is formed on the core particle containing an active ingredient.
- 43. The capsule according to claim 41, wherein the active ingredient is lansoprazole.

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- 44. The capsule according to claim 41, wherein the active ingredient is an optically active R-isomer of lansoprazole.
- 45. The capsule according to claim 41, wherein the 20 active ingredient is an optically active S-isomer of lansoprazole.
- 46. The capsule according to claim 41, wherein the core particle containing an active ingredient contains a stabilizer of basic inorganic salt.
- 47. The capsule according to claim 41, wherein the

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pH-dependently soluble release-controlled coating-layer of the tablet, granule or fine granule in which the release of soluble in the pH range of no less than 6.5, nor more than 7.0. a layer an active ingredient is controlled is

capsule according to claim 47, wherein the methacrylate-methacrylic acid copolymers having different release-controlled coating-layer methyl οĘ kinds more Ö two οĘ soluble mixture release properties. pH-dependently The ๗ contains

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The capsule according to claim 41, which further contains a gel-forming polymer. 49.

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(54) Title: CONTROLLED RELEASE PREPARATION

(57) Abstract: A controlled release preparation wherein the release of active ingredient is controlled, which releases an active ingredient for an extended period of time by staying or slowly migrating in the gastoninessinal tract, is provided by means such as capsulating a tablet, granule or fine granule wherein the release of active ingredient is controlled and a gel-forming polymer. Said tablet, granule or fine granule or fine granule of one granule has a release-controlled coating-layer formed on a core particle containing an active ingredient.

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According 1	According to international Patent Classification (IPC) or to both national classification and IPC	and IPC	
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×	Further documents are listed in the continuation of box C.	Patent family members are listed in ernex.	in armex.
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	Box I Observations when

This international Search Report has not been established in respect of certain claims under Articla 17(2)(a) for the following reasons:	
1. Claims Nos.: Decause they relate to subject matter not required to be searched by this Authority, namely:	
2. Claims Nos: because they relate to parts of the international Application that do not compty with the prescribed requirements to such an exident that no meaningful international Search can be carried out, specifically:	
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Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)	
The International Searching Authority found multiple inventions in this international application, as follows:	
see additional sheet	
1. As all required additional search fees were timely paid by the applicant, this international Search Report covers all scarchable dalms.	
2. $X$ As all searchable claims could be searched without effort justifying an additional fee, this Authority $dd$ not invite payment of any additional fee.	
3. As only some of the required additional search leas were timely paid by the applicant, this international Search Report covers only those claims for which fees were paid, specifically claims Nos	•
4. No required additional search fess were timely paid by the applicant. Consequently, this international Search Report is restricted to the Invention first mentioned in the claims, it is covered by claims Nos.:	
Remark on Protest  The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.	

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# Finis International Searching Authority found multiple (groups of) inventions in this international application, as follows: 1. Claims: 1-23 I. Claims: 1-23 Independent Claim id describes a capsule comprising a tablet, granule or fine granule, an active ingredient (not explicitly claimed) and a gel-forming polymer. 2. Claims: 24-40 Independent claim 24 describes a tablet, granule or fine granule comprising a core particle containing an imidazole compound (I'), a selected coating polymer which is soluble in the pit range of 6.0 to 7.5. 3. Claims: 41-49 Independent claim 41 describes a capsule comprising a core particle containing an indiazole compound (I'), a selected coating polymer which is soluble in the pit range of 6.0 to 7.5 and polymer which is soluble in the pit range of 6.0 to 7.5 arging polymer which is soluble in the pit range of 6.0 to 7.5 arging polymer which is soluble in the pit range of 6.0 to 7.5 arging polymer which is dissolved. (i) a tablet, granule or fine granule comprising a core particle containing an indiazole compound (I'), a selected coating which is dissolved. (ii) a tablet, granule or fine granule comprising a core particle containing an indiazole compound (I'), a selected coating which is dissolved.

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